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[THE NEW YORK STATE RESEARCH INSTITUTE, SARATOGA SPA]

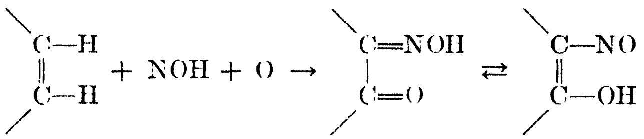
o-NITROSOPHENOLS. I. THE TYPICAL PROPERTIES OF *o*-NITROSOPHENOL AND ITS INNER COMPLEX METAL SALTS

GEORG CRONHEIM[1]

Received December 10, 1945

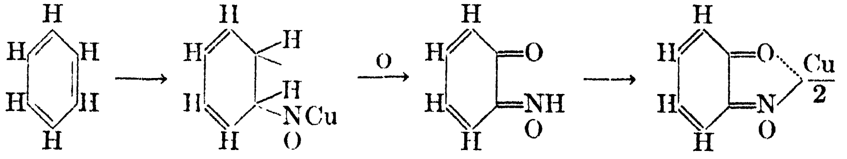
The number of *o*-nitrosophenols is surprisingly small. Besides *o*-nitrosophenol first prepared by Bayer (1) and later investigated in more detail by Baudisch and co-workers (2), no other member of this group is mentioned in the older literature except a few *o*-nitroso derivatives of polyvalent phenols. In more recent years 2-nitroso-5-aminophenol and 2-nitroso-5-halogenophenol have been prepared by Hodgson (3). The reason for this unpretentious number apparently lies in the fact that the preparation of *o*-nitrosophenols presents certain difficulties. The usual nitrosation of phenols with nitrous acid always leads to the *p*-nitroso compounds although Veibel (4) found that *o*-compounds are formed as intermediate products.

In several recent publications, Baudisch (5) has shown that by using the nitrosyl radical NOH and an oxidizing agent, it is possible to introduce in one reaction both a nitroso and a hydroxyl group into the benzene ring. The Baudisch reaction can be written schematically as follows:



The nitrosyl radical is formed either by reduction of nitrous acid or by oxidation of hydroxylamine. In addition, the presence of a copper salt is essential in this reaction, both to stabilize the NOH radical and to assure that an ortho- and not a para-nitrosophenol is formed.

According to Baudisch (6), some of the cupric ions are reduced to cuprous ions and form with the NOH radical, a complex of the type $[Cu^{I}NO]Cl$ which is paramagnetic (7) indicating that the NO group has one unpaired (free spinning) electron. This electron attacks an ethylene grouping in the benzene ring, and the intermediate is then oxidized to *o*-quinonemonoxime thereby breaking the bond between nitrogen and copper. The *o*-quinonemonoxime forms immediately an inner complex cupric salt which is very stable and prevents further oxidation to *o*-nitrophenol or rearrangement to *p*-nitrosophenol.



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[1] Present address: The S. E. Massengill Company, Bristol, Tenn.

If the Baudisch reaction is applied to phenol instead of benzene, the mechanism is essentially the same. However, due to the greater solubility of phenol in water, the reaction proceeds considerably faster and also with a better yield.

As can be expected for a reaction of this type, the actual yield of *o*-nitrosophenol is relatively small. Nevertheless, it was possible to prepare more than 50 new *o*-nitrosophenols in sufficient quantities to study certain characteristic properties of their metal salts.

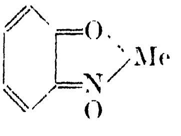
It is obvious that a detailed description of the very numerous observations on so many new, but closely related, compounds would include many unnecessary repetitions. To avoid this the results will be presented in the following three parts:

1. The typical properties of *o*-nitrosophenol and its inner complex metal salts.
2. New substituted *o*-nitrosophenols and some characteristic properties of their inner complex metal salts.
3. Some additional characteristics of substituted *o*-nitrosophenols.

Free *o*-nitrosophenol forms very volatile light green crystals soluble in organic solvents (Baudisch). In the presence of water, it shifts to the tautomer brown *o*-quinonemonoxime.

This can be demonstrated by shaking a solution of *o*-nitrosophenol in ether with successive portions of distilled water. After a short time the green ether solution suddenly changes its color to yellowish brown. On addition of one drop of very dilute hydrochloric acid, the color returns to green and can again be changed to brown by repeatedly shaking with water. This experiment can be carried out only with such organic solvents which like ether, ethyl acetate, amyl alcohol, and others, dissolve a small amount of water.

o-Nitrosophenol is distinguished by its ability to form strongly colored inner complex salts with heavy metals. Bayer (1) has mentioned the silver salt while Baudisch and co-workers (2) have described the copper, iron (III), cobalt, manganese, and aluminum salts which have the quinonemonoxime structure.



This is proved by two observations.

1. The copper salt of *o*-nitrosophenol can be obtained from the copper salt of *o*-hydroxy-N-nitrosophenylhydroxylamine (2).
2. The potassium salt of nitrosoresorcinol monoethyl ether gives upon treatment with ethyl iodide, the corresponding *o*-quinonemonoxime ether (8).

In addition to being typical for the *o*-nitrosophenol or *o*-quinonemonoxime grouping, these metal salts are furthermore characterized by the way in which they can be formed. In the earlier experiments, they were prepared by replacing a previously introduced alkali or alkaline earth with the corresponding heavy metal. However, it has been found in the present investigation that the affinity of the *o*-nitrosophenol for several metallic ions is so strong that it is sufficient to shake a solution of free *o*-nitrosophenol in petroleum ether with an aqueous salt solution, to form immediately and quantitatively, the corresponding nitrosophenol complex. This observation has served as the basis for studying certain properties of some of the known and for investigating new metal compounds of *o*-nitrosophenol.

The experiments were carried out in the following manner: The aqueous salt solution was shaken vigorously for a few seconds with an equal volume of the *o*-nitrosophenol solution in petroleum ether. After the two solvents had separated, the color and solubility of the complex formed were investigated. All salt solutions were of equimolar concentration (2.0×10^{-4}), and whenever possible, the *p*H was adjusted to 6.2–6.4. The salts investigated were the chlorides and/or acetates, sulfates, and nitrates of Ag^{+}, Al^{+++}, Au^{+++}, Cd^{++}, Co^{++}, Cr^{+++}, Cu^{++}, Fe^{++}, Fe^{+++}, Hg^{++}, Mn^{++}, Ni^{++}, Pb^{++}, Pd^{++}, Pt^{++}, Pt^{++++}, Sn^{++}, Ti^{+++}, U^{++}, Zn^{++}, and the cupferron salts of Al^{+++}, Ce^{+++}, Co^{++}, Cu^{++}, Hg^{++}, La^{+++}, Mn^{++}, Ni^{++}, Pd^{++}, Pr^{+++}, Ti^{+++}, U^{++}, Va^{+++}, Y^{+++}, Zn^{++}, and Zr^{++++}.

Most of these salts showed the formation of colored complexes with *o*-nitrosophenol regardless of the acid radical. No reaction could be detected with Sn^{++} and Cr^{+++} while the results with Al^{+++}, Pt^{++}, Pt^{++++}, Ce^{+++}, and La^{+++} were doubtful. Since Baudisch (2) had described the aluminum salt of *o*-nitrosophenol as almost black crystals, the affinity of *o*-nitrosophenol for the aluminum ion is apparently not strong enough to overcome the forces which hold the aluminum to negative acidic ions or water molecules. The same situation might apply also to the other negative or doubtful results.

The affinity of the various metallic ions for *o*-nitrosophenol differs greatly and suggests the following classifications:

1. *Metals with great affinity:*	*Color of very dilute solutions:*
(a) copper	reddish violet
mercury	reddish violet
nickel	red
iron (divalent)	green
(b) cobalt	grayish violet
palladium	green
2. *Metals with medium affinity:*	
zinc	pink
lead	pink
3. *Metals with little affinity:*	
iron (trivalent)	brown
silver, gold	
cadmium, manganese	
titanium	
uranium	reddish

The affinity of all metals of group 1 (a) and 1(b) is so great that the complexes are formed quantitatively by simply shaking the two solutions. This is all the more remarkable as the reactants are dissolved in separate immiscible liquid phases and their partition coefficients are very unfavorable toward the reaction between them. Based on this strong affinity new methods for the colorimetric determination of cobalt and divalent iron have been worked out by Cronheim and Wink (9). The cobalt determination has been further developed by Ellis and Thompson (10).

In group 2 are those metals which clearly react with *o*-nitrosophenol. However, judging from the light absorption of the resulting solution and from the amount of nitrosophenol used, the reaction is not quantitative. The metals in group 3 form a colored reaction product only if the salt concentration is increased from 10 to 100 times or if pyridine is present.

The solubility of the different metal complexes is so characteristic that it affords another means of classification. In order to simplify the presentation, only three solvents shall be considered, *viz.*, water, ether, and petroleum ether.

The cobalt, palladium (group 1b), and ferric complexes of *o*-nitrosophenol are soluble in both petroleum ether and ether and insoluble in water. The cupric, mercuric, ferrous, and nickel compounds (group 1a) are soluble in water and/or ether and insoluble in petroleum ether.

Concerning this latter group, its solubility in water and/or ether is governed by a simple rule. Being divalent ions, the existence of two nitrosophenol complexes can be expected.

$$\underset{\text{(Type I)}}{C_6H_4O_2N{-}Me{-}A} \quad \text{and} \quad \underset{\text{(Type II)}}{C_6H_4O_2N{=}Me{-}NO_2H_4C_6}$$

Both compounds exist for the four mentioned divalent metals. They can be distinguished and separated from each other by the fact that type II is always soluble in ether while type I is soluble only in water when A is Cl^-, SO_4^{--}, NO_3^- or CH_3COO^-. Although all complexes which have been described in the literature (Braudisch and co-workers) are of Type II, it has been found in the present study that compounds of Type I can be obtained just as easily as those of Type II. The relative excess of the free *o*-nitrosophenol or of the metallic ion determines which of the two types will be formed. This can be demonstrated in the following experiment.

If a small amount of *o*-nitrosophenol is shaken with an excess of a cupric salt, only compound I is formed, which is insoluble in ether. When the amount of *o*-nitrosophenol is gradually increased, the color of the aqueous solution deepens until all cupric ions have reacted to form compound I. After this first saturation point is reached, additional amounts of *o*-nitrosophenol will form compound II. In this stage, part of the copper complex can be shaken out with ether while part is soluble only in water. Finally the second saturation point will be reached, where only compound II is present, which is completely soluble in ether.

The complexes of Type I formed from the cupferron salts are all soluble in ether. This is not surprising, since their formulas closely resemble those of nitrosophenol complexes of Type II.

The *p*H is of greatest importance in the formation of all nitrosophenol metal complexes. This is shown by the color intensity obtained on shaking a given amount of a salt solution with a given amount of *o*-nitrosophenol at different *p*H (Figure 1).

It has already been mentioned that the nitrosophenol compounds of cobalt, palladium, and trivalent iron are soluble in petroleum ether. Several other complexes (Cu^{++}, Hg^{++}, Fe^{++}, Ni^{++}, Zn^{++}, Cd^{++}, Ti^{+++}) will become soluble through the addition of pyridine.

To demonstrate this "pyridine effect" a solution of cupric sulfate is shaken with an excess of *o*-nitrosophenol in petroleum ether to form the copper complex II. After adding a few drops of a 1% aqueous pyridine solution the mixture is shaken with the remaining or a fresh portion of *o*-nitrosophenol in petroleum ether. Upon separation of the two solvents the water is colorless, while the petroleum ether is colored reddish violet by a copper complex.

The mechanism of this effect is not clear. It is apparently characteristic for pyridine, since other organic bases like piperidine or piperazine do not have the same action. Moreover, it seems that in addition to the two nitrosophenols already present in the copper complex, one or more nitrosophenols are linked in the presence of pyridine by the secondary valences of the central copper atom, because an excess of free *o*-nitrosophenol is required. If the aqueous solution of the copper complex II is first freed from any excess of free *o*-nitrosophenol by shaking with pure petroleum ether the addition of pyridine is without effect.

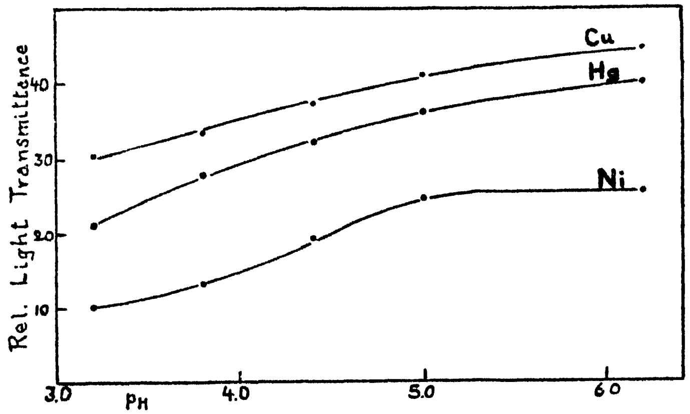


FIG. 1. INFLUENCE OF THE *p*H ON THE RELATIVE TRANSMITTANCE OF AQUEOUS SOLUTIONS OF *o*-NITROSOPHENOL SALTS

It has been stated previously that the acid radicals of the metal salts have no influence on the formation and properties of the corresponding nitrosophenol-metal compounds provided the *p*H is the same. This rule holds for inorganic acids and organic acids of low molecular weight, while organic acids of higher molecular weight may change the situation. This can be demonstrated in experiments with gluconates, phenolsulfonates, and phenylates, all of which possess a six-carbon skeleton, but of different structure.

The gluconates and phenolsulfonates behave exactly like the inorganic metal salts, *i.e.*, they form with *o*-nitrosophenol metal complexes of type I and II, soluble in water and ether respectively. On the other hand, the *o*-nitrosophenol salt of phenylmercuric nitrate is insoluble in water, but soluble in petroleum ether. This is particularly interesting, since the mercury-nitrosophenol complex of type II is not soluble in this solvent.

SUMMARY

The inner complex metal salts of *o*-nitrosophenol have been investigated. They include many new compounds most important of which are those of mercury, nickel, divalent iron, and palladium.

These salts as well as those of copper and cobalt formed from the *o*-quinonemonoxime are characterized by their color and their solubility in various solvents. The copper, mercury, nickel, and divalent iron complexes may exist both as mono- and di-quinonemonoxime compounds.

Saratoga Springs, N. Y.

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o-NITROSOPHENOLS. II. NEW SUBSTITUTED *o*-NITROSOPHENOLS AND CHARACTERISTIC PROPERTIES OF THEIR INNER COMPLEX METAL SALTS[1]

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In the previous part, *o*-nitrosophenol and its inner complex metal compounds were described (1). By applying the Baudisch reaction (2) to benzene and phenol derivatives, over 50 new mono- and di-substituted *o*-nitrosophenols could be prepared.

It is not intended to make a detailed survey of the literature of substituted *o*-nitrosophenols. Besides the previously mentioned nitrosophenol derivatives, such compounds as 4-nitrosoresorcinol, 5-nitrosohydroquinone and 2-nitrosophloroglucinol as well as some of their derivatives, are described in the older literature (3). There are only two observations on these compounds which have a direct relation to the present work. The first concerns the rearrangement of *o*-nitrosophenols into *o*-quinoneoximes and *vice versa*. Due to the much greater stability of the nitroso derivatives of resorcinol it is possible to obtain both isomeric forms in the solid state. Thereby, it has been found that the nitrosophenol form is always green while the quinoneoxime is always yellowish brown (4). This coincides with observations which have been described in the previous part.

The second interesting fact is the observation by Fèvre (1883) (5) that nitrosoresorcinol gives with ferrous sulfate, in aqueous solution, a characteristic green color which can be detected even in a dilution of 1 part in 10 million. The corresponding green ferrous compound of *o*-nitrosophenol has been introduced recently for the colorimetric estimation of divalent iron (6).

Monosubstituted o-nitrosophenols. In the present investigation, the Baudisch reaction was successfully applied to a number of monosubstituted benzene and phenol derivatives, summarized in Table I. Since the new compounds were "trapped" in the form of their reddish violet copper salts, there can be no question as to their having an *o*-nitrosophenol or *o*-quinonemonoxime chelate grouping. Consequently, if the starting material is an *o*- or *p*-substituted phenol, the configuration of the resulting *o*-nitrosophenol derivative is definite. It is only in the case of *m*-substituted phenols that two configurations are possible. The observations which form the basis for the (tentative) formulas assigned to these compounds in this table will be explained later in detail.

It can be seen that the list of monosubstituted *o*-nitrosophenols comprises almost every type of benzene derivative, thus showing the wide applicability of the Baudisch reaction. The compounds were selected with the purpose of investigating as many different types as possible and are not to be regarded as a systematic study of substituted *o*-nitrosophenols.

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TABLE I

o-NITROSOPHENOLS

PARENT COMPOUND	RESULTING *o*-NITROSOPHENOL DERIVATIVE	PARENT COMPOUND	RESULTING *o*-NITROSOPHENOL DERIVATIVE
Toluene	(3)-Methyl-6-nitrosophenol	Guaiacol	
o-Cresol	2-Methyl-6-nitrosophenol	Propiophenone	(3)-Propionyl-6-nitrosophenol
m-Cresol	(3)-Methyl-6-nitrosophenol	*o*-Propionylphenol	2-Propionyl-6-nitrosophenol
p-Cresol	4-Methyl-6-nitrosophenol	*p*-Propionylphenol	4-Propionyl-6-nitrosophenol
Ethylbenzene	(3)-Ethyl-6-nitrosophenol	Phenolphthalein	
o-Ethylphenol	2-Ethyl-6-nitrosophenol	Fluorobenzene	(3)-Fluoro-6-nitrosophenol
m-Ethylphenol	(3)-Ethyl-6-nitrosophenol	Chlorobenzene	(3)-Chloro-6-nitrosophenol
p-Ethylphenol	4-Ethyl-6-nitrosophenol	*o*-Chlorophenol	2-Chloro-6-nitrosophenol
p-Isopropylphenol	4-Isopropyl-6-nitrosophenol	*m*-Chlorophenol	(3)-Chloro-6-nitrosophenol
p-*tert*.-Butylphenol	4-*tert*.-Butyl-6-nitrosophenol	*p*-Chlorophenol	4-Chloro-6-nitrosophenol
p-*tert*.-Amylphenol	4-*tert*.-Amyl-6-nitrosophenol	Bromobenzene	(3)-Bromo-6-nitrosophenol
Phenylacetylene		*o*-Bromophenol	2-Bromo-6-nitrosophenol
o-Phenylphenol	2-Phenyl-6-nitrosophenol	*p*-Bromophenol	4-Bromo-6-nitrosophenol
o-Benzylphenol	2-Benzyl-6-nitrosophenol	*o*-Iodophenol	2-Iodo-6-nitrosophenol
p-Benzylphenol	4-Benzyl-6-nitrosophenol	Nitrosobenzene	
Benzyl alcohol		Nitrobenzene	
Salicylic alcohol	2-Hydroxy-3-nitrosobenzyl alcohol	Benzenesulfonic acid	
Salicylic acid	2-Hydroxy-3-nitrosobenzoic acid	Benzenesulfonamide	
p-Hydroxybenzoic acid	4-Hydroxy-3-nitrosobenzoic acid	Tyrosine	3-Nitroso-4-hydroxyphenylalanine
n-Propyl-*p*-hydroxybenzoate			

There are two groups of benzene derivatives in which the Baudisch reaction usually fails; namely, aromatic aldehydes and primary amines. In the case of amines, the reaction will lead to diazo compounds, while the aldehyde group reacts with the nitrosyl radical or with hydroxylamine directly to form hydroxamic acids or oximes respectively (Angeli reaction). Some exceptions will be mentioned later.

The properties of all substituted *o*-nitrosophenols are very similar to those of *o*-nitrosophenol. The free compounds can be shaken out with organic solvents from acidified aqueous solutions of their copper salts. Petroleum ether will dissolve readily all investigated *o*-nitrosophenols with the exception of those obtained from tyrosine, benzenesulfonamide, and sulfanilamide where ether or ethyl acetate is preferable.

The inner complex metal compounds which are so characteristic for the *o*-nitrosophenol (*o*-quinonemonoxime) grouping may be formed and investigated as previously described (1). Their outstanding properties (color and solubility) are summarized in Tables II and III.

It is quite apparent that all these salts, although very similar, are not absolutely uniform. In most cases the variations are not so much due to the substituent itself, but rather to its position relative to the *o*-nitrosophenol grouping. In order to simplify the following descriptions, the substituted *o*-nitrosophenols will be designated by the phenol from which they were obtained.

Outstanding among the variations is the color of the cobalt compounds in solution. All those obtained from ortho-substituted nitrosophenols are grayish violet, while all those obtained from meta- and para-substituted nitrosophenols are reddish brown. This rule has been verified in all cases where the substituent is an alkyl, phenyl, halogen, or carboxyl group.

A similar rule concerns the solubility of the cupric, mercuric, ferrous, and nickel salts. The complexes of type I are, under the outlined experimental conditions, without exception soluble in water. As to the complexes of type II, only those derived from ortho-substituted phenols are soluble in water, while those of meta- and para-substituted nitrosophenols are completely insoluble in both water and petroleum ether. In many cases, the metallic ions (especially copper and mercury) can thus be precipitated quantitatively even from highly dilute solutions.

The only seeming exceptions to this rule are alkyl nitrosophenols where the alkyl group contains three or more carbon atoms. These compounds will be described in greater detail in a following paper.

In the case of ferrous and nickel salts, the precipitation is not quantitative as indicated by the fact that the aqueous phase still is characteristically colored. Apparently the formation of the nitrosophenol complexes II does not proceed as easily as with copper and mercury, and the color of the water is due to some ferrous or nickel compounds of type I.

The solubility of the metal compounds of type II in organic solvents other than petroleum ether is not affected by substituents and is, therefore, the same as that of simple nitrosophenol salts.

TABLE II

Solubility in Water and Ether of the Two Types of Inner Complex Compounds of Monosubstituted *o*-Nitrosophenols with Copper, Mercury, Divalent Iron, and Nickel (Metals of Group Ia)

o-NITROSOPHENOL OBTAINED FROM	COMPLEX COMPOUND WITH															
	Cu^{++}				Hg^{++}				Fe^{++}				Ni^{++}			
	Color of complex compound															
	Red-violet				Red				Green				Red			
	Type of complex compound															
	I		II		I		II		I		II		I		II	
	Solubility in															
	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether
o-Cresol	+	−	+	+	+	−	+	+	+	−	+		+	−	+	
m-Cresol	+	−	−	+	+	−		+	+	−		+	+	−	+	+
p-Cresol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
o-Ethylphenol	+	−	+	+	+	−	+	+	+	−	+		+	−	+	
m-Ethylphenol	+	−	−	+	+	−		+	+	−		+	+	−	+	+
p-Ethylphenol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
p-Isopropylphenol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
p-*tert*.-Butyphenol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
p-*tert*.-Amylphenol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
Phenylacetylene	+				−		−	−	+		−	+	+			
o-Phenylphenol	+				+				+				+			
o-Benzylphenol. .	+				+				+				+			
p-Benzylphenol	+				+				+				+			
Benzyl alcohol	+	−		+	+	−			+	−			+	−		
Salicylic alcohol	+	−		+	+	−		+	+	−			+	−		
Benzoic acid	+	−		+	+	−		+	+	−			+	−		
o-Hydroxybenzoic acid	+	−		+	+	−		+	+	−			+	−		
p-Hydroxybenzoic acid.	+	−		+	+	−		+	+	−			+	−		
n-Propyl *p*-hydroxybenzoate	+				+				+				+			
Guaiacol	+				+				+				+			
Propiophenone	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
o-Propionylphenol .	+	−	+	+	+	−	+	+	+	−	+	+	+	−	+	+
p-Propionylphenol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
Phenolphthalein	+				+				+				+			
Fluorobenzene	+				+				+				+			
Chlorobenzene	+	−	−	+									+	−	+	+
o-Chlorophenol	+	−	+	+	+	−	+	+	+	−	+	−	+	−	+	+
m-Chlorophenol	+	−	−	+	+	−	−	+	+	−	+	+	+	−	+	+
p-Chlorophenol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
Bromobenzene	+												+			
o-Bromophenol	+	−	+	+	+	−	+	+	+	−	+	−	+	−	+	+
p-Bromophenol	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
o-Iodophenol	+	−	+	+	+	−	+	+	+	−	+	−	+	−	+	+
Nitrosobenzene	+				+				+				+			
Nitrobenzene	+				+				+				+			
Benzenesulfonic acid	+			+	+			+	+				+			
Benzenesulfonamide	+			+	+		−	−	+				+			
Tyrosine	+				+				+				+			

The "pyridine effect" (Table IV) likewise is in all cases the same as with simple *o*-nitrosophenol with one exception. All mercuric compounds of para-substituted nitrosophenols remain insoluble in petroleum ether even after addition of pyridine and in the presence of an excess of the free nitrosophenol. They can thus be differentiated from the corresponding cupric compounds.

All of the ferrous compounds show a positive pyridine effect. However, usually it is necessary to add the pyridine to the aqueous ferrous salt solution before shaking with the free nitrosophenol.

Another rule concerns the solubility of various lead complexes. The affinity of this metal towards most *o*-nitrosophenols is not very strong, the resulting solutions being only light pink in color. However, lead shows a characteristic pyridine effect, namely, the formation of a deep red precipitate with all para-substituted nitrosophenols. This effect was never observed with ortho- or meta-substituted nitrosophenols.

This reaction is very helpful in distinguishing between meta- and para-substituted nitrosophenols--a differentiation which cannot be made either by the color of the cobalt compounds or by the solubility of copper or mercury compounds. There is only one condition in which this reaction cannot be applied. A few substituted nitrosophenols (*o*- and *p*-bromonitrosophenol) have been found to possess very strong affinities for lead and to form directly the corresponding lead compounds, which are insoluble in water and petroleum ether. The precipitation seems to be quantitative and is not affected by the addition of pyridine.

Another interesting rule concerns the nitrosophenol complexes of trivalent iron, where not only the nature of the substituent, but also its position, is of importance. The affinity of ordinary *o*-nitrosophenol for ferric ions is so weak that the formation of the ferric complex which is soluble in petroleum ether can hardly be detected. The same is true for a number of substituted nitrosophenols (nitroso derivatives of *o*-chlorophenol, benzoic acid, salicylic acid, etc.) while others show very distinctly the formation of a ferric complex, soluble with brown color in petroleum ether. In all cases, where such a comparison could be made, it has been found that the meta- and para-substituted nitrosophenols result in much darker solutions with ferric salts than the ortho-substituted compounds. Whether this is due to differences in the color of the ferric complexes or differences in the affinity of the nitrosophenols to ferric ions, has not been investigated.

Of other metals with a selective affinity for substituted nitrosophenols only silver will be mentioned. It forms red precipitates with the nitrosophenols obtained from *p*-chloro- and *p*-bromo-phenol as well as from phenylacetylene.

From the foregoing it is evident that the nitroso derivatives of meta- and para-substituted phenols resemble each other rather closely in their metal compounds, but are distinctly different from ortho-substituted nitrosophenols. If one looks at the four possible configurations it appears probable that there should exist two groups of compounds, one in which the substituent R is in the immediate vicinity and another in which it is separated from the chelate

TABLE III

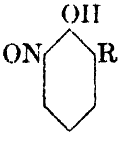
COLOR AND SOLUBILITY OF THE INNER COMPLEX COMPOUNDS OF MONOSUBSTITUTED *o*-NITROSOPHENOLS WITH COBALT, PALLADIUM, TRIVALENT IRON (METALS OF GROUP 1b), AND WITH ZINC, LEAD, AND SILVER (METALS OF GROUP 2)

o-NITROSOPHENOL OBTAINED FROM	COMPLEX COMPOUND WITH					
	Co^{++}	Pd^{++}	Fe^{+++}	Zn^{++}	Pb^{++}	Ag^{+}
	Color and solubility of metal complex in					
	Petroleum ether			Water		
o-Cresol	gray	green	very light brown			
m-Cresol	red brown	green	dark brown			
p-Cresol	red brown	green and precip.	dark brown		pink	
o-Ethylphenol	gray	green	very light brown			
m-Ethylphenol	red brown	green	dark brown			
p-Ethylphenol	red brown	green and precip	dark brown		pink	
p-Isopropylphenol	red brown		brown			
p-*tert*.-Butylphenol	red brown		brown	pink?		
p-*tert*.-Amylphenol	red brown		brown			
Phenylacetylene	gray	green	brown			brown precip.
o-Phenylphenol	gray	green	brown	pink?	pink	
o-Benzylphenol	gray	green				
p-Benzylphenol	red brown	green				
Benzyl alcohol	brown	green		pink	pink	
Salicylic alcohol	brown	green	pink	pink?	pink	
Benzoic acid	gray	green				
o-Hydroxybenzoic acid	gray	green				
p-Hydroxybenzoic acid	red brown	green		pink	pink	pink?
n-Propyl-*p*-hydroxybenzoate	red brown	green				
Guaiacol	red brown and precip.	green	brown			
Propiophenone	red brown and precip.	green and precip.	brown			
o-Propionylphenol	gray and precip.	green and precip.	brown and precip.	pink?	pink	

p-Propionylphenol	red brown and precip.	green and precip.	dark brown and precip.	pink?	pink	
Phenolphthalein ..	red brown	green and precip.	dark brown			
Fluorobenzene .. .	red brown					
Chlorobenzene . . .	red brown					red precip?
o-Chlorophenol .	gray	green	very light brown	pink?	pink?	pink?
m-Chlorophenol	red brown	green	dark brown	pink?	pink?	red precip.?
p-Chlorophenol	red brown	green and precip.	dark brown	pink	pink	
Bromobenzene .	gray					
o-Bromophenol .	gray	green and precip.	light brown	pink	red precip.	pink?
p-Bromophenol	red brown	green and precip.	dark brown	pink	red precip.	red precip.
o-Iodophenol .. .	gray	green		pink	pink	pink?
Nitrosobenzene. .	gray					
Nitrobenzene. ...	brown					
Benzenesulfonic acid .	gray	green and precip.	very light brown	pink?	pink	pink?
Benzenesulfonamide .	red brown	green				
Tyrosine	red brown					

"?" indicates that under the conditions used the formation of the metal complex is questionable.

grouping. Thus the similarity of the metal compounds of meta- and para-substituted nitrosophenols in contrast to ortho-substituted ones decides in favor of formula III for meta-substituted nitrosophenols. Accordingly, their general formula should be 3-R-6-nitrosophenol. Further evidence as to the correctness of this formula, will be given in a subsequent paper, together with the formulas of alkyl substituted nitrosophenols which were obtained directly from the benzene instead of the phenol derivatives.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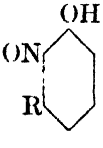
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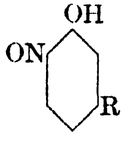
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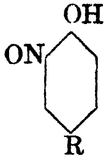
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TABLE IV

"Pyridine Effect" of Monosubstituted *o*-Nitrosophenols

Upon addition of Pyridine the metal complex
becomes soluble in petroleum ether +
remains insoluble in petroleum ether –
forms a red precipitate P

o-NITROSOPHENOL OBTAINED FROM·	COMPLEX COMPOUNDS FORMED WITH:								
	Cu^{++}	Hg^{++}	Fe^{++}	Ni^{++}	Zn^{++}	Pb^{++}	Ag^{+}	Cd^{++}	Ti^{+++}
o-Cresol	+	+	+	+	+	–			
m-Cresol	+	+	+	+	+	–			
p-Cresol	+	–	+	+	+	P			
o-Ethylphenol	+	+	+	+	+	–			
m-Ethylphenol	+	+	+	+	+	–			
p-Ethylphenol	+	–	+	+	+	P			
p-tert.-Butylphenol					+	P			
Phenylacetylene	+	–	+	+	+	P			+
o-Phenylphenol	+	+	+	+	+		?	+	+
Salicylic alcohol	+	+	+	+					
Salicylic acid	+	+	+	+					?
Guaiacol	+	+	+	+					
Propiophenone	+		+	?					
o-Propionylphenol	+	+	+	+					
p-Propionylphenol	+	–	+	?		P			
Fluorobenzene	+	+	+	+					
o-Chlorophenol	+	–	+	+	+	–			
m-Chlorophenol	+	–	+	+		–	+		
p-Chlorophenol	+	–	+	+	+	P		+	
o-Bromophenol	+	–	+	+	+	–	–	+	+
p-Bromophenol	+	–	+	+	+	–	–	+	+
Nitrobenzene	+		+	+					
Benzenesulfonamide	+	+	+	+				+	

"?" indicates that under the conditions used the formation of the metal complex is questionable.

Disubstituted o-nitrosophenols. Heretofore, only nitrosophenols with one substituent have been mentioned. The Baudisch reaction can, however, be applied successfully also to benzene and phenol derivatives with more than one substituent. Examples are given in the following list of compounds all of which formed the corresponding *o*-nitrosophenols (Table V).

The number of these compounds is not very great but sufficient to prove two points (Tables VI–VIII):

1. Even if the benzene ring contains two substituents, either of the same or of different kinds, it is possible to introduce by means of the Baudisch reaction, a hydroxyl and a nitroso group.

TABLE V

DISUBSTITUTED *o*-NITROSOPHENOLS

PARENT COMPOUND	RESULTING *o*-NITROSOPHENOL DERIVATIVE
o-Xylene	(3,4)-Dimethyl-6-nitrosophenol
3,4-Dimethylphenol	3,4-Dimethyl-6-nitrosophenol
3-Methyl-4-chlorophenol	3-Methyl-4-chloro-6-nitrosophenol
m-Xylene	(2,4)-Dimethyl-6-nitrosophenol
2,4-Dimethylphenol	2,4-Dimethyl-6-nitrosophenol
3,5-Dimethylphenol	3,5-Dimethyl-6-nitrosophenol
p-Xylene	2,5-Dimethyl-6-nitrosophenol
2,5-Dimethylphenol	2,5-Dimethyl-6-nitrosophenol
5-Methyl-2-isopropylphenol	5-Methyl-2-isopropyl-6-nitrosophenol
2,4-Diamylphenol	2,4-Diamyl-6-nitrosophenol
2,3-*tert*.-Dibutyl-4-methylphenol	(2,3)-*tert*.-Dibutyl-4-methyl-6-nitrosophenol
o-Diphenylbenzene	(3,4)-Diphenyl-6-nitrosophenol
o-Fluorotoluene	
m-Fluorotoluene	
p-Fluorotoluene	
m-Chlorotoluene	
p-Chlorotoluene	
o-Dichlorobenzene	
p-Chlorobromobenzene	
o-Nitroanisole	
o-Nitrobenzaldehyd	
Sulfanilamide	

2. The presence of more than one substituent does not alter the typical properties of the *o*-nitrosophenol chelate grouping.

Concerning the various dimethylnitrosophenols (nitrosoxylenoles) a more detailed description will be given in a subsequent paper.

In the list of disubstituted benzene derivatives are two compounds belonging to those two groups which usually do not form an *o*-nitrosophenol in the Baudisch reaction. These two compounds are *o*-nitrobenzaldehyde and sulfanilamide, representing aldehydes and primary aromatic amines respectively. The reason for the atypical behavior is obvious in the case of *o*-nitrobenzaldehyde. It is known that this compound exists in two isomeric forms, one of which has lost completely its aldehyde character. It is probably the latter which reacts in the Baudisch reaction to form a substituted *o*-nitrosophenol.

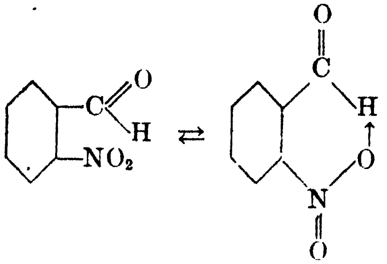

TABLE VI

Solubility in Water and Ether of the Two Types of Inner Complex Compounds of Disubstituted *o*-Nitrosophenols with Copper, Mercury, Divalent Iron, and Nickel (Metals of Group 1a)

o-NITROSOPHENOL OBTAINED FROM:	COMPLEX COMPOUND WITH															
	Cu^{++}				Hg^{++}				Fe^{++}				Ni^{++}			
	Color of complex compound															
	Red-violet				Red				Green				Red			
	Type of complex compound															
	I		II		I		II		I		II		I		II	
	Solubility in															
	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether	Water	Ether
3,4-Dimethylphenol	+				+		−	+	+				+		−	+
2,4-Dimethylphenol	+				+				+				+			
3,5-Dimethylphenol	+		−	+	+		−	+	+		−	+	+		−	+
2,5-Dimethylphenol	+				+				+				+			
2,4-Diamylphenol	+				+				+				+			
Thymol	+	−	−	+	+	−	−	+	+	−	−	+	+		−	+
o-Diphenylbenzene	+				+				+				+			
o-Fluorotoluene	+				+				+				+			
m-Fluorotoluene	+				+				+				+			
p-Fluorotoluene	+				+				+				+			
m-Chlorotoluene	+				+				+				+			
p-Chlorotoluene	+				+				+				+			
3-Methyl-4-chlorophenol	+		−	+	+		−	+	+		−	+	+		−	+
o-Dichlorobenzene	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
p-Chlorobromobenzene	+				+				+				+			
o-Nitroanisole	+	−			+				+	−			+	−		
o-Nitrobenzaldehyde	+				+				+							
Sulfanilamide	+			+	+				+				+			

Preparation of p-substituted o-nitrosophenols. The fact that copper salts of type II of all *p*-substituted nitrosophenols are insoluble in water can be utilized for the preparation of these compounds. The principle consists in the nitrosation of a *p*-substituted phenol in the presence of the proper amount of a cupric salt and the maintenance of the correct *p*H. The formed nitrosophenol immediately combines with the cupric ion and is thus precipitated as an almost pure copper salt.

TABLE VII

COLOR AND SOLUBILITY OF THE INNER COMPLEX COMPOUNDS OF DISUBSTITUTED *o*-NITROSOPHENOLS WITH COBALT, PALLADIUM, TRIVALENT IRON (METALS OF GROUP 1b), AND WITH ZINC, LEAD, AND SILVER (METALS OF GROUP 2)

o-NITROSOPHENOL OBTAINED FROM:	COMPLEX COMPOUND WITH					
	Cu^{++}	Pd^{++}	Fe^{+++}	Zn^{++}	Pb^{++}	Ag^{+}
	Color and solubility of metal complex in					
	Petroleum Ether			Water		
3,4-Dimethylphenol	red brown	green	light brown	pink?		
2,4-Dimethylphenol	brown					
3,5-Dimethylphenol	gray	green	brown	pink	pink?	pink?
2,5-Dimethylphenol	brown					
2,4-Diamylphenol	brown	green				
Thymol	gray			pink	pink?	
o-Diphenylbenzene	gray					
o-Fluorotoluene	red brown		brown	pink?		
m-Fluorotoluene	brown					
p-Fluorotoluene	brown					
m-Chlorotoluene	gray	green	brown	pink	pink	
p-Chlorotoluene	brown		light brown?	pink	pink	
3-Methyl-4-chlorophenol	brown	green	light brown?	pink	pink	
o-Dichlorobenzene	red brown	green	brown	pink	red precip.	pink
p-Chlorobromobenzene	brown		light brown	pink	pink	
o-Nitroanisole	gray	green	light brown	pink	pink	pink?
o-Nitrobenzaldehyde	gray	green				
Sulfanilamide	red brown		light brown			

"?" indicates that under the conditions used the formation of the metal complex is questionable.

Twelve and nine-tenths grams (0.1 mole) of *p*-chlorophenol is dissolved in 30 ml. of glacial acetic acid. This solution is diluted with 50 ml. of water and sufficient sodium acetate is added to bring the *p*H to 4.2. To this mixture is added a solution of 17.3 g. (0.25 mole) of sodium nitrite and 12.5 g. (0.05 mole) of crystalline cupric sulfate in 500 ml. of water. The mixture turns deep green immediately and then darkens quickly. After several days standing at room temperature, the precipitated copper salt of 4-chloro-6-nitrosophenol can be filtered off. About 50% of the theoretical amount will be formed during the first three days. The total yield reaches about 80–85% after two weeks. The dried crude precipitate is about 90% pure and can be recrystallized from an alcohol-chloroform (2:3) mixture.

Anal. Calc'd for $C_{12}H_6Cl_2CuN_2O_4$: Cl, 18.8; Cu, 16.9.

Found: Cl, 19.0; Cu, 16.7.

The free chloronitrosophenol in crystalline form can be obtained in the following manner: The copper salt is suspended in normal sulfuric acid and shaken repeatedly with petroleum ether. These extracts are washed twice with ice-water and then shaken with a small amount of normal sodium hydroxide solution. Upon careful neutralization of the ice-cold solution of the sodium salt with normal sulfuric acid the free chloro-*o*-quinonemonoxime is precipitated in the form of small yellowish brown needles. They are filtered off, washed with ice-water and dried in the desiccator; m p. 40–41° uncorr.

The same procedure has been applied with equally good results to form the copper salts and the free *o*-nitrosophenols, respectively from *p*-cresol and *p*-bromophenol.

TABLE VIII

"PYRIDINE EFFECT" OF DISUBSTITUTED *o*-NITROSOPHENOLS

Upon addition of pyridine the metal complex
becomes soluble in petroleum ether +
remains insoluble in petroleum ether —
forms a red precipitate P

o-NITROSOPHENOL OBTAINED FROM.	COMPLEX COMPOUNDS FORMED WITH								
	Cu^{++}	Hg^{++}	Fe^{++}	Ni^{++}	Zn^{++}	Pb^{++}	Ag^{+}	Cd^{++}	Ti^{+++}
3,4-Dimethylphenol	+	+	+	+	?	—			
2,4-Dimethylphenol	+	+	+	+	P	P			
3,5-Dimethylphenol	+	+	+	+	P	P	?	?	?
Thymol					+	+			
o-Diphenylbenzene	+	+	+	+					
o-Fluorotoluene	+	+	+	+					
m-Fluorotoluene	+	+	+	+					
m-Chlorotoluene	+	+	+	+	+	P			
p-Chlorotoluene	+	+	+	+	+	—			
3-Methyl-4-chlorophenol	+	+	+	+	+	P			+
o-Dichlorobenzene	+	+	+	+	+	—	?		
p-Chlorobromobenzene	+	+	+	+	+	—			
o-Nitroanisole	+	+	+	+					
Sulfanilamide	+		+	+					

"?" indicates that under the conditions used the formation of the metal complex is questionable.

Anal. Calc'd for $C_{14}H_{12}CuN_2O_4$: Cu, 18.95. Found: Cu, 18.5.
The free *o*-nitrosophenol $C_7H_7NO_2$, had the m.p. 56–58° uncorr.
Anal. Calc'd for $C_{12}H_6Br_2CuN_2O_4$: Br, 34.4. Found: Br, 34.9.
The free *o*-nitrosophenol, $C_6H_4BrNO_2$, had the m.p. 51–53° uncorr.

SUMMARY

By using the Baudisch reaction 33 new mono- and 19 new di-substituted *o*-nitrosophenols have been prepared and some of their inner complex metal salts have been investigated. The color and the solubility of these metal complexes show very definite relationships to the configuration of the substituted *o*-nitrosophenols.

SARATOGA SPRINGS

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o-NITROSOPHENOLS. III. SOME ADDITIONAL CHARACTERISTICS OF SUBSTITUTED *o*-NITROSOPHENOLS[1]

GEORG CRONHEIM[2]

Received December 10, 1945

In a previous paper (1), it had been mentioned that the Baudisch reaction has been applied successfully to a number of mono- and di-alkyl-benzenes and -phenols with formation of the corresponding *o*-nitrosophenols. The list included the following compounds:

Toluene	*o*-, *m*-, *p*-Cresol
Ethylbenzene	*o*-, *m*-, *p*-Ethylphenol
	p-iso-Propylphenol
	p-*tert.*-Butylphenol
	p-*tert.*-Amylphenol
o-Xylene	3,4-Dimethylphenol
m-Xylene	2,4-Dimethylphenol
	3,5-Dimethylphenol
p-Xylene	2,5-Dimethylphenol
	3-Methyl-6-isopropylphenol (thymol)
	2,4-Diamylphenol
	3,4-Di-(*tert.*-butyl)-5-methylphenol

The properties of the corresponding *o*-nitrosophenols are in general those described previously. The only exception concerns certain metal salts of alkyl-substituted nitrosophenols where the alkyl group contains three or more carbon atoms. It had been stated that the complexes of copper, mercury, nickel, and divalent iron with two para-substituted *o*-nitrosophenols (Type II), are insoluble in both water and petroleum ether. Under the conditions used they appeared, therefore, as characteristically colored flocculent precipitates. However, if the substituent in the *o*-nitrosophenol is an alkyl group with three or more carbon atoms these metal salts (Type II) become soluble in petroleum ether. The metal complexes with one nitrosophenol (Type I) are not affected, that is, they are soluble only in water.

Although all the investigated nitroso compounds in this group are obtained from para-substituted phenols, it seems unlikely that the altered solubility of the metal salts is due to this configuration. It is much more probable that it is caused by the number of carbon atoms in the side chain which overcomes the influence of the quinonemonoxime (nitrosophenol) grouping in a similar manner as in the phenylmercuric-*o*-nitrosophenol salts mentioned in an earlier paper (2). This special solubility behavior has been used by Baudisch and Heggen (3) in their colorimetric determination of iron with 4-*tert*.-butyl-6-nitrosophenol.

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[1] The author is greatly indebted to J. F. Thompson and I. R. McCartney of the U. S. Plant, Soil, and Nutrition Laboratory in Ithaca, N. Y. for the transmittance curves which are mentioned in this paper.

[2] Present address: The S. E. Massengill Company, Bristol, Tenn.

From a systematic standpoint, the group of alkyl-substituted *o*-nitrosophenols is more complete than any other group. Therefore, certain deductions can be made with regard to the mechanism of the Baudisch reaction and the configuration of the resulting *o*-nitrosophenols.

If the Baudisch reaction is applied to a monosubstituted benzene derivative other than a phenol, the resulting monosubstituted *o*-nitrosophenols can have any one of four configurations. By applying the previously described rules concerning the formation, solubility, color, etc., of the different metal salts, it is possible to determine in a very simple manner which of these isomers has actually been formed.

TABLE I

CHARACTERISTICS OF VARIOUS METAL SALTS OF SUBSTITUTED *o*-NITROSOPHENOLS OBTAINED FROM CRESOLS AND TOLUENE

METALLIC ION	*o*-CRESOL	*m*-CRESOL	*p*-CRESOL	TOLUENE
Cu^{++}	Red violet	Red violet	Red violet precip.	Red violet
Fe^{++}	Green	Green	Green, part. precip.	Green
Fe^{+++}	Yellowish brown	Dark brown	Dark brown	Dark brown
Co^{++}	Grayish violet	Red brown	Red brown	Red brown
Hg^{++}	Red	Red	Red	Red
Pb^{++} plus pyridine			Red precip.	

A typical example is given by toluene and the three cresols. The most important observations with the nitrosophenols obtained from these four compounds are summarized in Table I. Those for the ethyl derivatives are identical.

From these results, it seems evident that the *o*-nitrosophenol formed from toluene is identical with that formed from *m*-cresol. According to the previously outlined consideration, it is, therefore, probably 3-methyl-6-nitrosophenol.

In order to verify this conclusion the transmittance spectra of the four products were measured.[3] The curves for the three nitrosocresols are shown in Figure 1. They are characterized by a maximum of transmittance at 340 mμ and by a minimum which lies at 410, 400, and 390 mμ respectively for the nitroso derivatives of *o*-, *m*-, and *p*-cresol. The curve for the nitrosophenol obtained from toluene corresponds to that of nitroso-*m*-cresol, as can be seen in Table II which lists the relative transmittance values for all four compounds in the important range from 300 to 430 mμ.

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[3] These and the following transmittance curves were determined in a Beckman Spectorphotometer with 1-cm. absorption cells. Wherever possible, the concentration of the compounds measured has been indicated. In those cases in which the concentration is not exactly known, the curves are reproduced only as a further characterization of the various compounds.

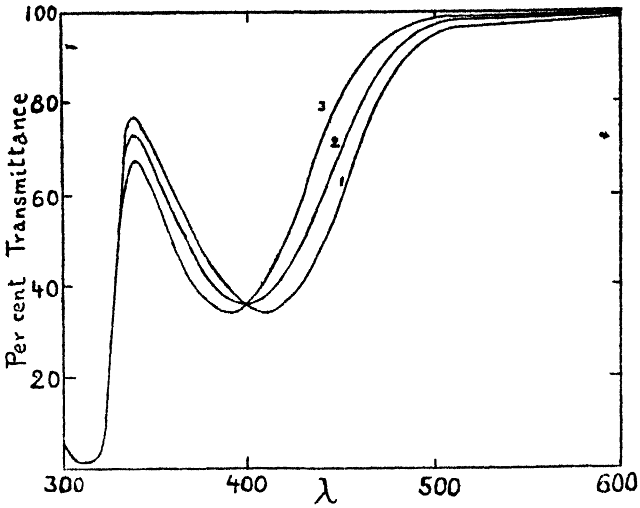


FIG. 1. TRANSMITTANCE CURVES OF THE *o*-NITROSOPHENOLS OBTAINED FROM 1) ORTHO- 2) META-, AND 3) PARA-CRESOL

TABLE II
RELATIVE TRANSMITTANCE VALUES OF LIGROIN SOLUTIONS OF SUBSTITUTED *o*-NITROSOPHENOLS OBTAINED FROM CRESOLS AND TOLUENE

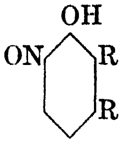
λ IN mμ	*o*-CRESOL	*m*-CRESOL	*p*-CRESOL	TOLUENE
300	5.5	5.4	5.1	7.8
310	1.0	1.1	1.2	1.1
320	3.0	3.2	3.5	3.1
325	17.4	18.1	17.6	15.4
330	54.0	56.2	52.2	56.2
335	73.0	72.8	66.4	71.7
340	$\boxed{77.4}$	$\boxed{77.8}$	$\boxed{68.4}$	$\boxed{75.9}$
350	71.2	67.8	59.0	67.0
360	61.5	57.0	49.3	58.0
370	54.0	49.3	42.2	48.8
380	45.2	41.1	35.8	41.0
390	39.1	36.6	$\boxed{33.7}$	37.3
400	35.8	$\boxed{35.9}$	35.8	$\boxed{35.5}$
410	$\boxed{34.0}$	38.2	41.5	37.7
420	36.8	42.3	51.7	43.3
430	42.0	51.3	61.6	51.4

Maximum of transmittance ⬚ .

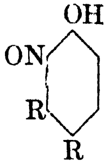
Minimum of transmittance ▭ .

The previous paper (1) contains several more examples which have shown similar results although not quite as clearly. For instance, the cobalt, copper, mercury, and silver salts of the chlorobenzene derivative seem to be identical with those of *m*-chloronitrosophenol.

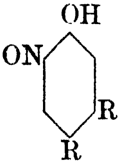
In the case of a dialkylbenzene, six isomeric *o*-nitrosophenols are possible provided the two alkyl groups are identical.



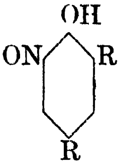
I



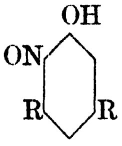
II



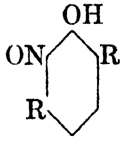
III



IV



V



VI

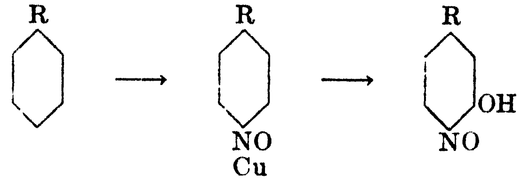
If one starts from corresponding phenols, the configuration of the resulting *o*-nitrosophenol is definite in all cases except II and III which both might be formed from 3,4-dialkylphenol.

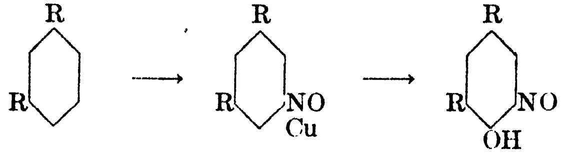
In the present study, the three xylenes and five of the possible six dimethylphenols were investigated. The series was complete with the exception of 2,3-dimethylphenol. 2,6-Dimethylphenol was included, but as expected, did not form an *o*-nitrosophenol because both places adjacent to the phenol group are occupied. The reaction proceeded well with 3,5-dimethylphenol while in all other cases, the yield of the corresponding *o*-nitrosophenol was very small.

Of special interest are the results for the nitrosophenol derivatives of *m*-xylene. As can be expected, the properties of the two possible compounds (IV and V) are very similar. The absorption spectra are almost identical. There is, however, a difference of about 10 mμ in the wave length of maximum absorption. Whether or not this represents an actual variation or is due to some impurity has not been decided.

As to the metal complexes of the two nitrosophenols there are very slight differences in the colors of the cobalt, copper, nickel, and mercury salts. Using these variations, an attempt was made to identify the *o*-nitrosophenol obtained for *m*-xylene. Since all four above mentioned metal complexes of the *m*-xylene derivative had exactly the same characteristics as those of IV, it seems justified to formulate this compound as 2,4-dimethyl-6-nitrosophenol. This represents a case where the position of both the nitroso and hydroxyl group has been directly identified.

This latter result together with the formation of 3-alkyl-6-nitrosophenol from alkyl benzenes offers an interesting aspect concerning the mechanism by which these compounds are formed. Baudisch (4) has shown that the formation of *o*-nitrosophenols from aromatic hydrocarbons with ethylene groupings proceeds in two steps. First a copper-nitrosyl-complex is added to the benzene ring with subsequent oxidation of an adjacent hydrogen to a hydroxyl group. For a mono- and di-alkylbenzene, the two steps can schematically be written as follows:

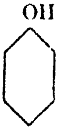
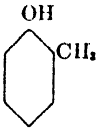
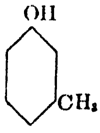
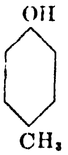
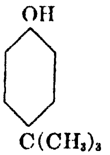
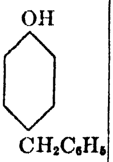
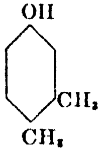
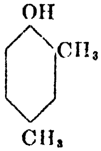
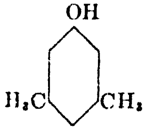
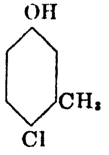




The similarity in the two reactions is apparent: In both cases, the nitroso group enters the benzene ring as far away from the alkyl group as possible. The same rule seems to apply also to other substituents notably, chlorine, bromine, etc.

TABLE III

Maximum of Light Transmittance of Substituted *o*-Nitrosophenols

o-NITROSOPHENOL OBTAINED FROM:	NUMBER OF SUBSTITUENTS BESIDES NITROSOPHENOL GROUPING	WAVE LENGTH OF MAXIMUM LIGHT TRANSMITTANCE, mμ
	0	330
    	1	340
   	2	350

In addition to the different nitrosocresols mentioned, the absorption spectra of several other mono- and di-substituted nitrosophenols have been determined. Essentially, they are all alike except for slight changes in the positions of the absorption maximum and minimum in the near ultraviolet. The results arranged in Tables III and IV indicate:

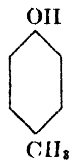
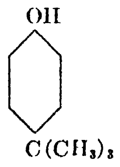
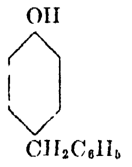
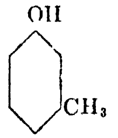
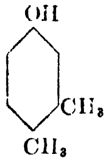
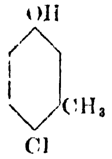
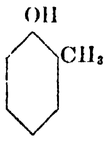
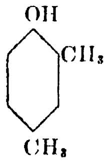
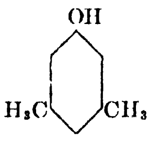
1. The wave length of the minimum absorption increases with the number of substituents in the benzene ring (Table III).

2. The wave length of the maximum absorption depends upon the distance between the hydroxyl group and the nearest substituents other than the nitroso group (Table IV).

The presence of a second substituent and its position relative to either the hydroxyl or the nitroso group seems to be without great influence. The only compound which cannot be classified in this scheme is 3,5-dimethyl-6-nitrosophenol.

TABLE IV

Minimum of Light Transmittance of Substituted *o*-Nitrosophenols

o-NITROSOPHENOLS OBTAINED FROM:	POSITION OF NEAREST SUBSTITUENT RELATIVE TO HYDROXYL GROUP	WAVE LENGTH OF MINIMUM LIGHT TRANSMITTANCE, mμ
  	para	390–395
  	meta	400–405
 	ortho	410–420
		430

A number of transmittance curves for some of the metal compounds of various *o*-nitrosophenols were also determined. Since such curves give a much better characteristic of the color of these complexes, they are shown in the Figures 2–5.[3]

In the preceding papers, it has been stated that the solutions of ferrous nitrosophenol complexes are green, while those of the ferric compounds are brown.

A more detailed study revealed, however, that under proper conditions, both green and brown solutions may be obtained from both ferrous and ferric salts.

The simplest method is to use different solvents for the free *o*-nitrosophenol. If *p*-bromonitrosophenol is dissolved in petroleum ether, ether, or acetone, the solution of its ferric complex is dark brown while it is green if ethyl, butyl or isoamyl alcohol is used as the solvent. On the other hand, the dark green percipitate of the ferrous complex of *p*-bromonitrosophenol dissolves in alcohol with green and in ether with brown color.

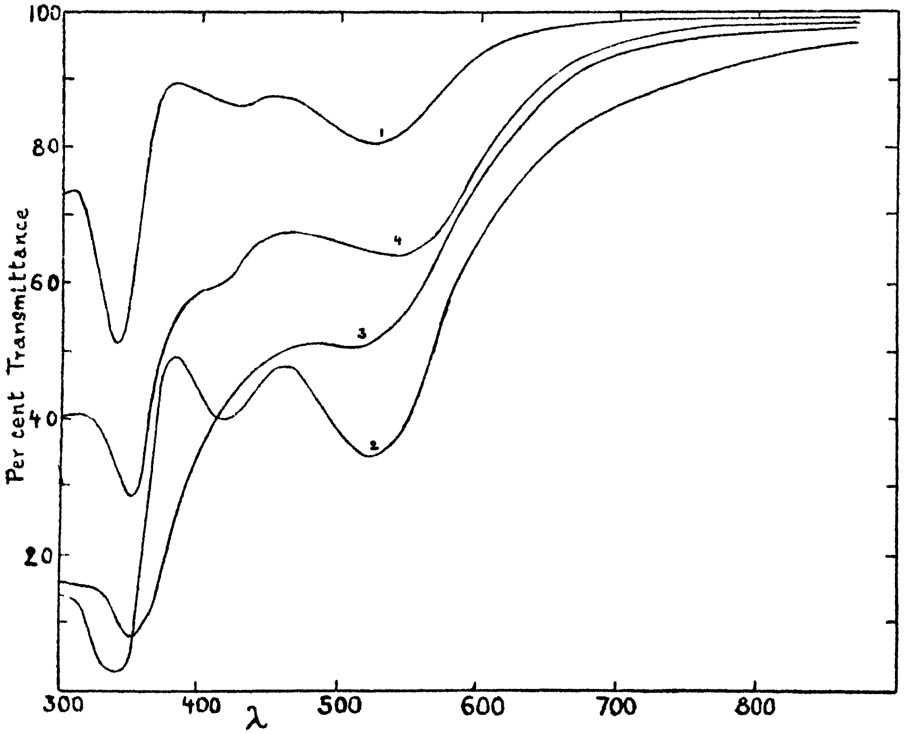


FIG. 2. TRANSMITTANCE CURVES OF THE CUPRIC SALTS OF 1) *o*-NITROSOPHENOL (2 γ/ML.) 2) *o*-NITROSOPHENOL (10 γ/ML), 3) 4-*tert.*-BUTYL-6-NITROSOPHENOL, AND 4) 3,5-DIMETHYL-6-NITROSOPHENOL

Furthermore, it is even possible to change the color of the different iron complexes after they have already been formed. If *o*-nitrosophenol in petroleum ether is shaken with an aqueous ferrous salt solution, the usual green ferrous complex is formed, soluble in water. If then a few drops of dilute hydrochloric acid is added and the whole mixture is shaken again, the petroleum ether takes on a distinct brown color while the aqueous layer remains green. The same experiment has been performed with *o*- and *p*-bromonitrosophenol. The brown color does not appear if the nitrosophenol solution is shaken only with dilute hydrochloric acid in the absence of a divalent iron salt.

The corresponding change can also be produced with the brown ferric complex.

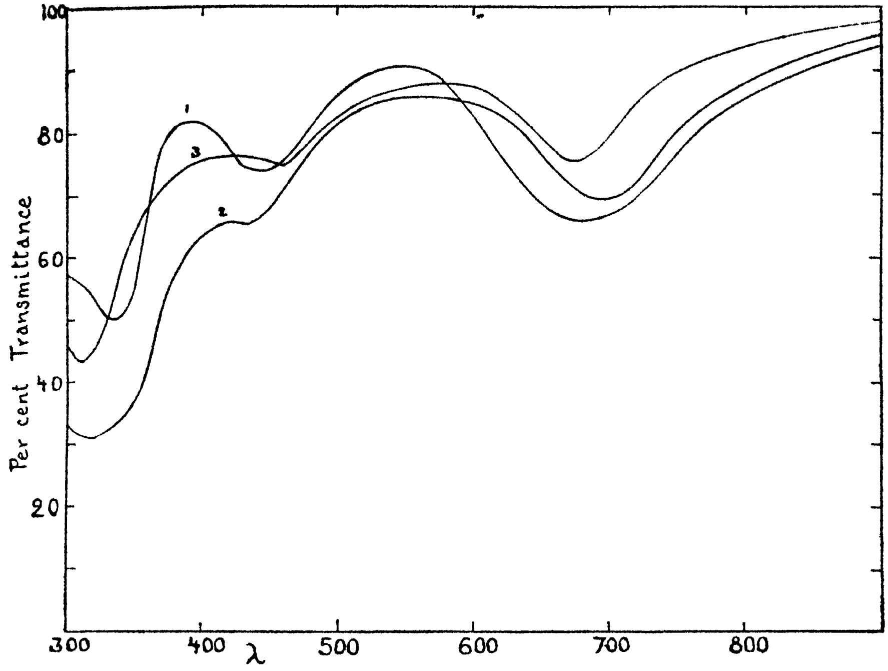


FIG. 3. TRANSMITTANCE CURVES OF THE FERROUS SALTS OF 1) *o*-NITROSOPHENOL (4 γ/ML.), 2) 4-*tert*.-BUTYL-6-NITROSOPHENOL, AND 3) 3,5-DIMETHYL-6-NITROSOPHENOL

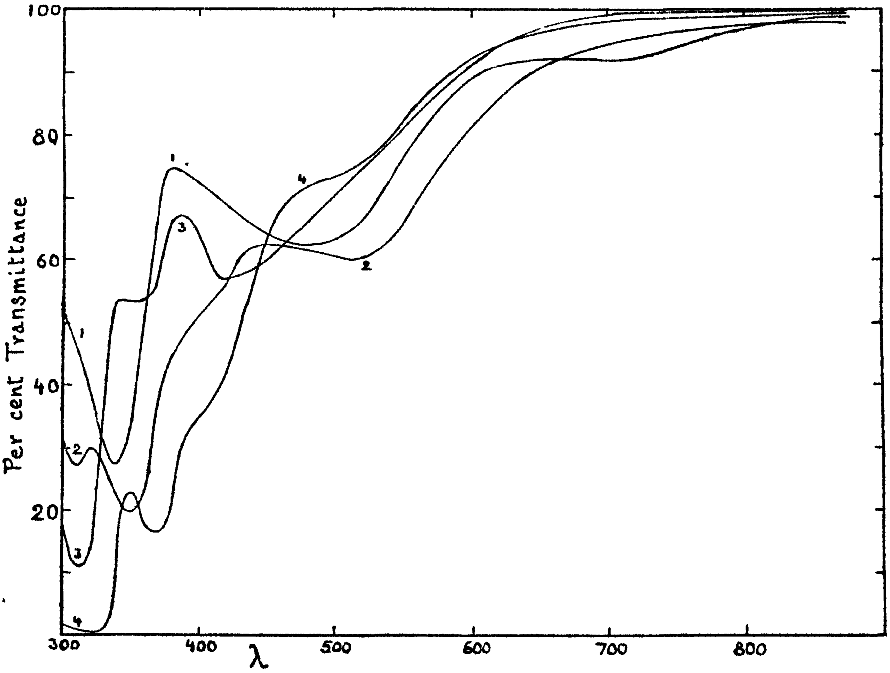


FIG. 4. TRANSMITTANCE CURVES OF THE MERCURIC SALTS OF 1) *o*-NITROSOPHENOL (10 γ/ML.), 2) 4-*tert*.-BUTYL-6-NITROSOPHENOL, 3) 3,5-DIMETHYL-6-NITROSOPHENOL (10 γ/ML.), 4) 3-METHYL-4-CHLORO-6-NITROSOPHENOL (10 γ/ML.)

If *p*-bromonitrosophenol in petroleum ether is shaken with an aqueous ferric salt solution, the petroleum ether becomes deep brown. If then pyridine is added and the mixture is shaken again, the color of the petroleum ether solution changes to a brilliant green. The same change has been observed by using the nitrosophenols obtained from *m*- and *p*-cresol.

It is not yet possible to give a satisfactory explanation for all these observations. The experiments seem to indicate that once the iron complex is formed, the central iron atom changes its valence rather easily. Furthermore, the direction of this electron transfer seems to be influenced by the dipole moment of the solvent and by the presence of compounds with a strong acid or basic character.

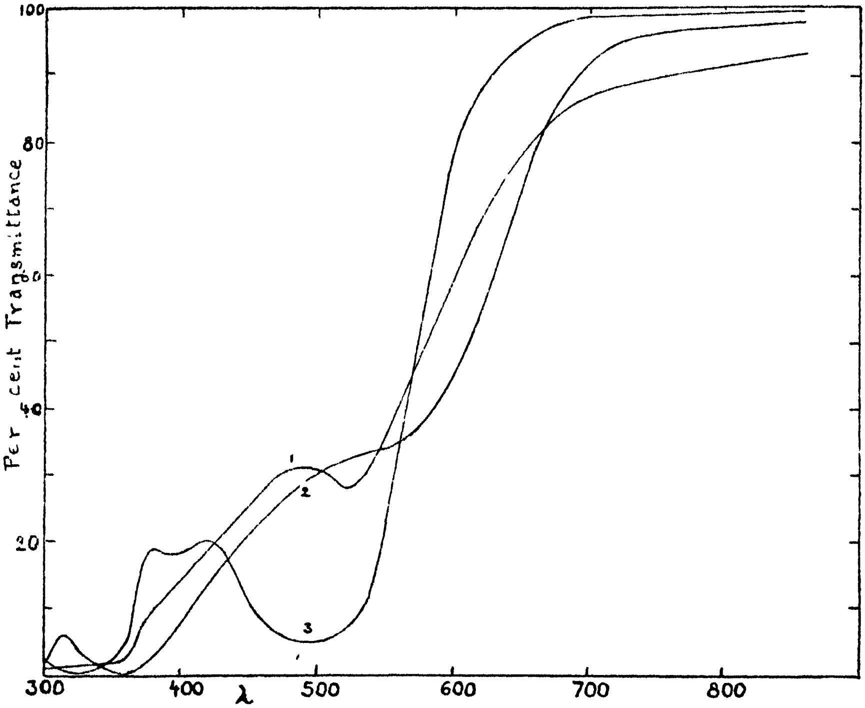


FIG. 5. TRANSMITTANCE CURVES OF THE 1) ZINC SALT, 2) COBALT SALT, AND 3) NICKEL SALT OF 4-*tert*.-BUTYL-6-NITROSOPHENOL

SUMMARY

The structural formulas of alkyl-substituted *o*-nitrosophenols obtained from alkylbenzenes have been established. The determination has been made based on the color and solubility of their inner complex metal salts and the absorption spectra of the free substituted *o*-nitrosophenols.

Some additional properties of the inner complex compounds of *o*-nitrosophenols with di- and tri-valent iron have been described.

Saratoga Springs, N. Y.

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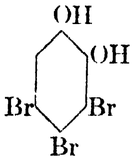
[Contribution from the Chemical Laboratory of the Academy of Commerce]

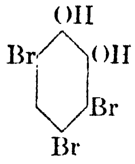
THE REDUCTION OF BROMO DERIVATIVES OF CATECHOL, RESORCINOL, AND PYROGALLOL

MORITZ KOHN[1] AND LUDWIG STEINER

Received December 18, 1945

In the course of investigations of the reduction of brominated phenols (1) by zinc dust in acetic acid, among the dihydroxybenzenes a series of hydroquinone derivatives was studied. It developed, however, that brominated catechols also are attacked in the same reaction with extraordinary ease and rapidity. Thus, from tetrabromocatechol, even by quite brief action of zinc dust and acetic acid, a tribromocatechol (m.p. 106°) was obtained, which was characterized by preparation of its dimethyl ether (m.p. 69°) and its diacetate (m.p. 141°). The existence of two isomeric tribromocatechols can be predicted, 1,2-dihydroxy-3,4,5-tribromobenzene (I) and 1,2-dihydroxy-3,4,6-tribromobenzene (II).


I


II

I is the 3,4,5-tribromocatechol of m.p. 139°, dimethyl ether m.p. 86°, which is obtained by direct bromination of catechol (2). There can therefore be no doubt that the above described tribromocatechol is the 3,4,6-tribromocatechol (II). Observations in the Vienna laboratory have shown that in debromination of brominated phenols with zinc and acetic acid, bromine atoms ortho to the hydroxyl are replaced by hydrogen with special ease. It was therefore from the outset to be expected that in this case also an ortho bromine would be replaced, which would give I, a presumption that did not hold.[2]

Tetrabromoguaiacol (III) is also debrominated with extreme ease, with formation of a dibromoguaiacol. On the basis of previous experiences, it was to be expected that two bromine atoms para to each other would be removed, as was actually the case. The dibromoguaiacol obtained melted at 94°, and is therefore identical with 4,5-dibromoguaiacol (IV) (3). This was confirmed by methylation, which yielded 4,5-dibromoveratrole (V) (4) of m.p. 92°.

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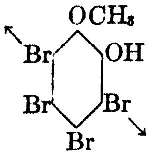
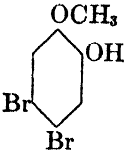
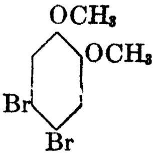
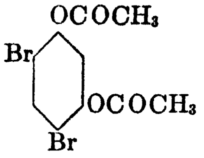
[2] In the reductive acetylation of tetrabromocatechol with zinc dust and acetic anhydride, Kohn and Pfeifer (1 a) obtained a dibromocatechol diacetate of m.p. 173°. Purely by analogy, the substance was regarded as 3,5-dibromocatechol diacetate. The results of the present investigation, showing that a bromine para to a hydroxyl can be removed, casts doubt on the structure of the 173° acetate.


III


IV

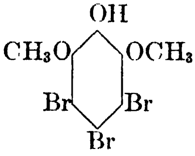

V

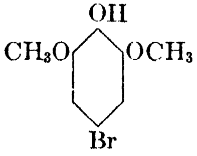

VI

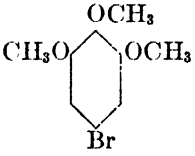
In the reductive acetylation of 2,4,6-tribromoresorcinol, Kohn and Pfeifer (1 a) obtained a dibromoresorcinol diacetate of m.p. 94°. This was regarded as 4,6-dibromoresorcinol diacetate (VI), formed by replacement of the bromine between the two hydroxyls by hydrogen. Proof of the validity of this assumption can now be offered; boiling 2,4,6-tribromoresorcinol with zinc dust and acetic acid gave 4,6-dibromoresorcinol, which was further identified through its dimethyl ether (5) of m.p. 141°. Acetylation of 4,6-dibromoresorcinol gave the same diacetate as that from the reductive acetylation of tribromoresorcinol.

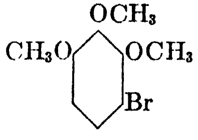
With other reducing agents, as sulfites or stannous chloride, tribromoresorcinol behaves quite differently. Davis and Harrington (6) established that under these conditions the bromine between the hydroxyls did not exchange.

4,5,6-Tribromopyrogallol 1,3-dimethyl ether (VII) (7) exchanges two bromine atoms for hydrogen with zinc dust and acetic acid, with formation of a new monobromopyrogallol dimethyl ether. Here also was to be expected that the bromine para to the hydroxyl would not be removed, and that 5-bromopyrogallol 1,3-dimethyl ether (VIII) would result. That this is actually so was shown by methylation, which gave a compound which must be 5-bromopyrogallol trimethyl ether (IX), since it is a solid (m.p. 78°), whereas the isomeric 4-bromopyrogallol trimethyl ether (X) (7, 8) is a liquid.


VII


VIII


IX


X

That the 5-bromo compound would melt higher than the 4-bromo would be expected from the symmetrical structure of the molecule. This fact is also in agreement with the observation of Gräbe and Suter (9) with the two isomeric chloropyrogallol trimethyl ethers. The 5-chloro ether is solid, whereas the 4-chloro ether is liquid.

EXPERIMENTAL

3,4,6-Tribromocatechol (II). Ten grams of tetrabromocatechol (10) in 30 cc. of glacial acetic acid, with 10 cc. of water and 8 g. of zinc dust, was refluxed for 4 minutes with continuous shaking. The filtered liquid, on dilution with water, precipitated a solid, which was recrystallized from boiling water; thin needles of m.p. 106°.

Anal. Calc'd for $C_6H_3Br_3O_2$: C, 20.7; H, 0.86.

Found: C, 21.14; H, 1.06.

By methylation with alkali and dimethyl sulfate, 3,4,6-tribromoveratrole was obtained, which crystallized from alcohol in needles of m.p. 69°.

Anal. Calc'd for $C_8H_7Br_3O_2$: C, 25.6; H, 1.86; Br, 64.0; $2OCH_3$, 16.5.
Found: C, 25.65; H, 1.98; Br, 63.6; OCH_3, 16.63.

3,4,6-Tribroveratrole boils without appreciable decomposition at 315–317° (uncorr.)/736 mm. The distillate, crystallized from alcohol, melted at 69°.

3,4,6-Tribromocatechol diacetate. 3,4,6-Tribromocatechol was refluxed 5 hours with five times its weight of acetic anhydride. It was poured into water, filtered, and crystallized from alcohol; prismatic needles, m.p. 141°.

Anal. Calc'd for $C_{10}H_7Br_3O_4$: C, 27.84; H, 1.62.
Found: C, 28.17; H, 1.71.

4,5-Dibromoguaiacol (IV) from tetrabromoguaiacol (III). Ten grams of tetrabromoguaiacol (II) with 30 cc. of glacial acetic acid, 10 cc. of water, and 8 g. of zinc dust was refluxed for 5 minutes. On filtration into water, an oil separated, which solidified in a few hours. The solid was dried in a vacuum and recrystallized from ligroin with the use of charcoal; m p. 94°.

Anal. Calc'd for $C_7H_6Br_2O_2$: C, 29.76; H, 2.12.
Found: C, 29.71; H, 2.49.

Methylation of the dibromoguaiacol gave the known 4,5-dibromoveratrole (V) of m.p. 92°.

Anal. Calc'd for $C_8H_8Br_2O_2$: C, 32.43; H, 2.72; 2 OCH_3, 20.9.
Found: C, 32.46; H, 2.74; OCH_3, 21.06.

4,6-Dibromoresorcinol from 2,4,6-tribromoresorcinol. Thirty grams of 2,4,6-tribromoresorcinol in 20 cc. of acetic acid with 30 cc of water and 25 g. of zinc dust was refluxed for 12 minutes. It was filtered into water, and salted out with sodium chloride. The white needles were recrystallized from water, m.p 112°. Methylation and recrystallization from alcohol gave 4,6-dibromoresorcinol dimethyl ether of m.p 141°. Acetylation of 4,6-dibromoresorcinol gave the diacetate (from alcohol) of m.p. 94°.

5-Bromopyrogallol 1,3-dimethyl ether (VIII) from tribromopyrogallol 1,3-dimethyl ether (VII). Twenty grams of tribromopyrogallol 1,3-dimethyl ether in 35 cc. of acetic acid and 40 cc. of water with 20 g of zinc dust was refluxed for 45 minutes. It was poured into water, and the oil which separated solidified after several hours in a freezing mixture. The product was recrystallized from boiling dilute acetic acid, dried in a vacuum, and recrystallized from ligroin; woolly needles of m.p. 106°.

Anal. Calc'd for $C_8H_9BrO_3$: C, 41.2; H, 3.86, Br, 34.33.
Found: C, 41.57; H, 3.89; Br, 34.02.

The *benzoyl derivative* crystallized from alcohol, m.p. 119°.

Anal. Calc'd for $C_{15}H_{13}BrO_4$: C, 53.4; H, 3.85; Br, 23.73.
Found: C, 53.33; H, 3.90; Br, 23.64.

5-Bromopyrogallol trimethyl ether (IX). On methylation of 5-bromopyrogallol 1,3-dimethyl ether, an oil separated, which became solid when shaken. After dilution with water, it was recrystallized from dilute alcohol, then from petroleum ether; m.p. 78°.

Anal. Calc'd for $C_9H_{11}BrO_3$: C, 43.73; H, 4.42.
Found: C, 43.94; H, 4.61.

The substance boiled at 269–273° (uncorr.)/747 mm.; (the b.p. of tribromopyrogallol trimethyl ether is 341° (uncorr.)/759 mm.).

SUMMARY

1. The action of zinc dust and acetic acid on tetrabromocatechol gives 3,4,6-tribromocatechol through replacement of a bromine para to a hydroxyl by hydrogen.

2. Tetrabromoguaiacol, by replacement of two para situated bromine atoms, gives 4,5-dibromoguaiacol.

3. 2,4,6-Tribromoresorcinol suffers replacement of the bromine between the two hydroxyls, to give 4,6-dibromoresorcinol.

4. Tribromopyrogallol 1,3-dimethyl ether exchanges the two bromine atoms meta to the hydroxyl for hydrogen, giving 5-bromopyrogallol 1,3-dimethyl ether.

VIENNA, AUSTRIA

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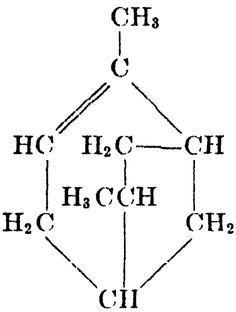
[CONTRIBUTION FROM IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

STUDIES IN THE TERPENE SERIES. VI. CYCLIC ISOMERIZATION OF LIMONENE (1)[1]

V. N. IPATIEFF, HERMAN PINES, VLADIMIR DVORKOVITZ, R. C. OLBERG, AND MICHAEL SAVOY

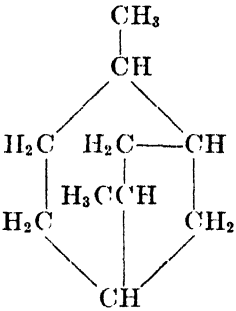
Received April 8, 1946

During the study of the polymerization of limonene with silicophosphoric acid catalyst "Solid Phosphoric Acid" (2) at an elevated temperature under atmospheric pressure, it was found that the products formed consisted, to a large extent, of isomeric bicyclic monoterpenes $C_{10}H_{16}$ and tricyclic diterpenes $C_{20}H_{32}$. Based upon the experimental evidence to be cited, it was suggested that the unsaturated bicyclic terpene is composed largely of a new terpene containing a five- and a six-membered ring (Formula I).



(I)

2,6-Dimethyl-bicyclo-(3,2,1)-2-octene



(II)

2,6-Dimethyl-bicyclo-(3,2,1)-octane

The cyclic isomerization of limonene was accompanied by side reactions which greatly complicated the investigation of the structure of the bicyclic terpenes.

When limonene was passed over silicophosphoric acid at 200° and a liquid hourly space velocity of two, 35% of polymeric and 65% of monomeric hydrocarbons were obtained. The monomeric hydrocarbons were composed mainly of unreacted limonene, *p*-cymene, dihydrolimonene, and bicyclic terpenes with some admixture of bicyclic dihydroterpenes. The presence of *p*-cymene indicated that a hydrogen transfer reaction similar to the one reported previously (3) had occurred.

A complete conversion of limonene was achieved when the monomeric fraction was repassed over the same catalyst; this seems to be an effective method of freeing the reaction product of monocyclic terpenes.

For the removal of *p*-cymene, a portion of the monomer was selectively hydrogenated under pressure with nickel-kieselguhr catalyst (4) at 40–50°. Under these conditions, only the olefinic hydrocarbons underwent hydrogenation, while the aromatic hydrocarbons remained unchanged. The aromatic hydrocarbons were removed from the saturated monomer by sulfur dioxide extraction, followed by treatment with fuming sulfuric acid. It was found that the monomer contained 30% of *p*-cymene, which was identified by ultraviolet absorption spectra and solid derivatives.[2] The aromatic-free hydrogenated product consisted of a mixture of bicyclic dihydroterpenes (Formula II) and 1-methyl-4-isopropylcyclohexane. The latter was separated from the mixture by selective dehydrogenation (5) to *p*-cymene, followed by extraction with fuming sulfuric acid. By this procedure, it was established that the hydrogenated product contained 25% of 1-methyl-4-isopropylcyclohexane.

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[1] This work was financed in part by Universal Oil Products Company.

Presented in part by V. N. Ipatieff and V. Dvorkovitz before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, September 8-12, 1941.

The product that remained after dehydrogenation and extraction consisted of bicyclic dihydroterpenes and was distilled on a fractionation column of an efficiency of fifty theoretical plates at a reflux ratio of 50:1. The distillation curve is given in Graph III. The various fractions were analyzed and their physical properties were investigated. The data obtained showed that the products consisted of bicyclic hydrocarbons. According to infrared analysis, the two largest fractions boiling at 162–164°, and 164–168°, and constituting sixty per cent of the bicyclic terpenes, were composed principally of the same compoud, each, however, mixed with small amounts of some other hydrocarbons, possibly stereoisomers.

The validity of the proposed Formula II, which was suggested for the hydrogenated bicyclic terpene obtained from the isomerization of limonene, was determined by destructive hydrogenation. For that reason an investigation of the action of hydrogen (1) upon compounds of bicyclic dihydroterpene type of known structures was undertaken. The results of this investigation indicated that bicyclic dihydroterpenes containing rings of five and six members are cleaved by hydrogen less readily than those of three- and four-membered rings. Thus, isocamphane and isobornylane required a temperature of 210° to effect ring fission. The destructive hydrogenation of the bicyclic dihydroterpenes obtained from limonene likewise required a high temperature indicating the absence of three- or four-membered rings. The products of the reaction consisted mainly of alkyl cyclopentanes and a small amount of alkyl cyclohexane.

In order to show the existence of a five-membered ring in the bicyclic dihydroterpene obtained from limonene, the product was treated with dilute aqueous magnesium chloride solution. It was reported previously (6) that while isocamphane and isobornylane are stable in the presence of dilute aqueous magnesium chloride even at 425°, pinane, a bicyclic dihydroterpene containing a four-membered ring, readily underwent ring cleavage at 280–350° and resulted in the formation of monocyclic olefinic hydrocarbons. Application of this technique to the unknown bicyclic dihydroterpenes lent further evidence to the proposed five- and six-membered rings. No reaction occurred even at 400°.

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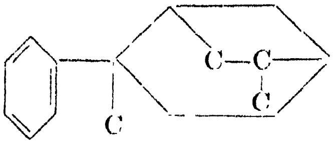
[2] The formation of *p*-cymene in this reaction caused us to investigate the purity of limonene and dipentene used in this study. It was found that limonene did not contain any traces of aromatics while dipentene contained 22% of *p*-cymene. These results caused us to use only limonene in this investigation even though silicophosphoric acid catalyst yielded the same products with dipentene as with limonene; *p*-cymene present in dipentene did not take part in the reaction; only the concentration of *p*-cymene in the two cases was different.

The presence of a six-membered ring in the unknown bicyclic dihydroterpene was further substantiated by dehydrogenation over platinized asbestos. At 290–300° a small amount of the total product consisted of aromatic hydrocarbons. *p*-Cymene was identified in the reaction product.

In order to determine the position of the double bond in the unsaturated bicyclic terpenes obtained from limonene, some of the fractions were oxidized either by ozone or by dilute potassium permanganate. In each case, a good yield of a keto acid was obtained, which on further oxidation with bromine in alkaline solution gave a quantitative yield of carbon tetrabromide and a dicarboxylic acid. The oxidation of the low-boiling isomers with selenium dioxide yielded an aldehyde, indicating again that the methyl group was adjacent to the carbon atom containing a double bond. A complete study of the degradative oxidation of the isomer is planned and this investigation will be described later.

An attempt was made to condense the various unsaturated monomeric fractions, obtained from the isomerization of limonene, with benzene in the presence of sulfuric acid. The lowest-boiling isomers did not react with benzene.[3] According to molecular weight and analysis it consisted of bicyclic hydrocarbons C_9H_{14}. In view of the small amount of the hydrocarbon available, it was impossible to study it any further.

The fraction boiling above 162° reacted with benzene in the presence of sulfuric acid to form tricyclic hydrocarbons which, on the basis of the proposed Formula I, may have the following structure:



On the basis of all the evidence presented in this paper, it can be concluded that the proposed structure for the bicyclic isomer formed from limonene (Formula I) is the most plausible one. Further study of the structure of the bicyclic isomer produced is in progress.

It was decided to repeat the experiments of Carter, Smith, and Read (7) who treated limonene with 85% orthophosphoric acid for 128 hours at room temperature. These authors found that besides polymerization only isomeric monocyclic terpenes were formed. It was also found by us that polymerization was the chief reaction; only 12% of a product, distilling at 168–175°, was obtained; the latter contained a mixture of monocyclic terpenes and 22% of *p*-cymene.

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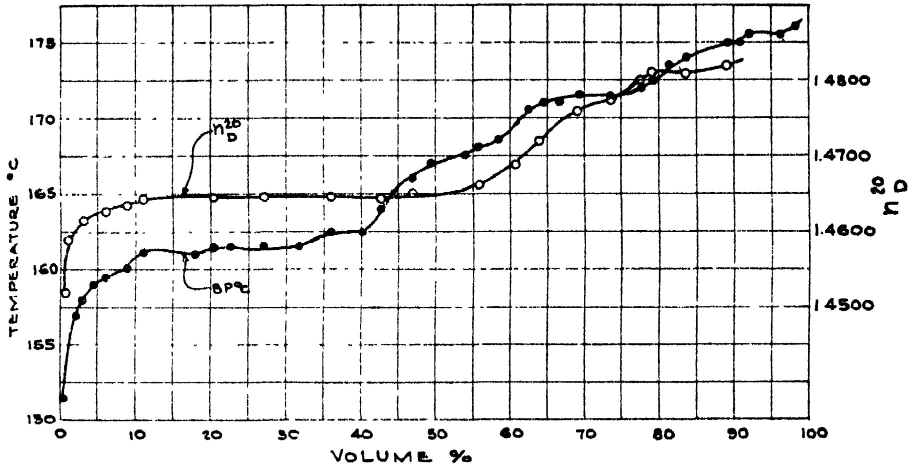
[3] A similar phenomenon was noticed previously by us (6) when an attempt was made to cause benzene to react with 1-ethyl-2-isopropylcyclopentene obtained through ring fission of pinane

The presence of bicyclic terpenes was not observed. The monocyclic terpenes on hydrogenation were converted to *p*-menthane; this indicated that cycloisomerization of limonene did not occur.

EXPERIMENTAL PART

A. *Once-through passage.* Freshly distilled limonene, n_D^{20} 1.4722, $[\alpha]_D^{23}$ + 123.1°, was passed over 75 g. of silicophosphoric acid ("Solid Phosphoric Acid") catalyst of 4–8 mesh size at 200° and at atmospheric pressure at a rate of 150 ml. per hour. The monomeric hydrocarbons were separated from the polymers by steam distillation, which was carried out in the presence of sodium hydroxide in order to decompose any phosphoric acid ester which might have been formed during the reaction. The steam distillate, consisting of 65% by weight of the total hydrocarbons, was dried over calcium chloride and distilled on a column of an efficiency of fifty theoretical plates. The boiling point curve and the index of refraction of the distillate is given in Graph I.



GRAPH · I

Analyses of the monomeric fractions, b.p. 153–176°. The percentage of unreacted limonene was determined by hydrogenating 30 g. of the product in the presence of a coprecipitated copper oxide-aluminum oxide catalyst (65% Cu and 35% Al_2O_3). The hydrogenation was carried out in a 450-ml. capacity rotating autoclave at 90° and under an initial hydrogen pressure of 100 atmospheres. Under these conditions, only the double bond in the side chain underwent hydrogenation. The hydrogenation was considered terminated when the pressure remained constant for 1.5 hours and when 2 ml. of the hydrogenated product dissolved in 4 ml. of benzene to which a few drops of 96% sulfuric acid were added, gave a yellow coloration to the acid layer. Where small amounts of limonene were present, the color of the acid became dark brown. From the amount of hydrogen absorbed, it was calculated that the monomeric product contained 19.5% of unreacted limonene.

The amount of olefins in the monomeric fraction was determined by selective hydrogenation of an aliquot portion by using nickel-on-kieselguhr catalyst with 50 atm. of hydrogen pressure at 40–50°. No hydrogenation of the benzenoid ring occurs under these conditions. From the total hydrogen absorbed and from knowledge of the previously determined diolefin content, the amount of monoolefins present could be calculated. The hydrogen absorbed corresponded to a monoolefin concentration of 10%.

The amount of aromatic hydrocarbons was determined by extracting the product, obtained from the selective hydrogenation, with fuming sulfuric acid.

Twenty-six grams of the monomeric fraction dissolved in an equal volume of *n*-pentane was hydrogenated in a 450-ml. capacity rotating autoclave, using 2.5 g. of nickel-kieselguhr catalyst (4). Twenty-six ml. of the hydrogenated product, which was free of olefins as determined by a dilute potassium permanganate test, was treated at 0° with 52 ml. of fuming sulfuric acid which contained 15% of sulfur trioxide. The 18 ml. of saturated hydrocarbons that remained after two such treatments indicated that 30% of aromatic hydrocarbons was present in the original sample. This analysis checked with that obtained by ultraviolet absorption; the latter also indicated that the aromatic hydrocarbons formed consisted of *p*-cymene only.

In order to determine and separate the dicyclic hydrocarbons from the menthane produced by hydrogenation, 12 g. of the saturated hydrocarbons, free from *p*-cymene, was selectively dehydrogenated by passing it thrice over 35 ml. of 8–14 mesh platinized alumina at 250° and at a rate of 7 ml. per hour. From the amount of hydrogen liberated and from the amount of aromatic hydrocarbons formed by catalytic dehydrogenation, it was found that the saturated product contained 55% of dicyclic hydrocarbons, $C_{10}H_{18}$, which boiled at 164–165° and had n_D^{20} 1.4507.

Anal. Calc'd from $C_{10}H_{18}$[4] C, 86.87; H, 13.13.
Found: C, 87.24; H, 12.82.

On the basis of the results obtained, it was calculated that the monomer fraction consisted of 21% limonene, 10% dihydrolimonene, 30% *p*-cymene, and 39% bicyclic terpene.

B. *The recyclic procedure.* The monomeric fraction separated from once-through passage of limonene over silicophosphoric acid catalyst, as described above, was again passed over the same catalyst at 200°. The benzene-sulfuric acid color test did not reveal any unreacted limonene in the resulting product which was distilled on a column of an efficiency of 50 theoretical plates and at reflux ratio of 50:1. The boiling range and the index of refraction of the various cuts are given in Graph II. The distribution of the various types of hydrocarbons in the different fractions was determined by selective hydrogenations, extractions, and dehydrogenations as described in detail in the investigation of the product of once-through passage. The results of this investigation are given in the following table.

	BOILING RANGE, °C		
	160–165	165–170	170–175
Bicyclic terpenes, %	63	46	25
Cyclic monoolefins, %	22	17	28
p-Cymene, %	15	37	47

Reaction with benzene. The condensation of the various fractions with benzene was carried out in a 300-ml. capacity three-necked flask provided with a dropping-funnel, mercury-sealed stirrer, and a reflux condenser. One part by volume of 96% sulfuric acid and one part of benzene were placed in the flask which was cooled to 4°. To this was added, dropwise, a solution consisting of one part of benzene and one part of a monomeric fraction obtained from the cycloisomerization of *d*-limonene. After all the hydrocarbons were added, the mixture was stirred for an additional one-half hour. Two layers were formed; the upper layer, composed of hydrocarbons, was separated, washed with water, aqueous sodium hydroxide, water, dried over calcium chloride, and distilled.

Fraction b.p. 156–159°, n_D^{20} 1.4568. Twenty-six grams of the product was treated with benzene. Eleven grams of bicyclic terpene boiling at 42–46° at 12 mm., n_D^{20} 1.4528 was separated from the upper layer after the removal of benzene. This product of hydrogenation at 50°, in the presence of a nickel-kieselguhr catalyst yielded bicyclic dihydroterpenes which distilled at 155–158°, n_D^{20} 1.4506, d_4^{20} 0.8485. It did not contain any aromatics.

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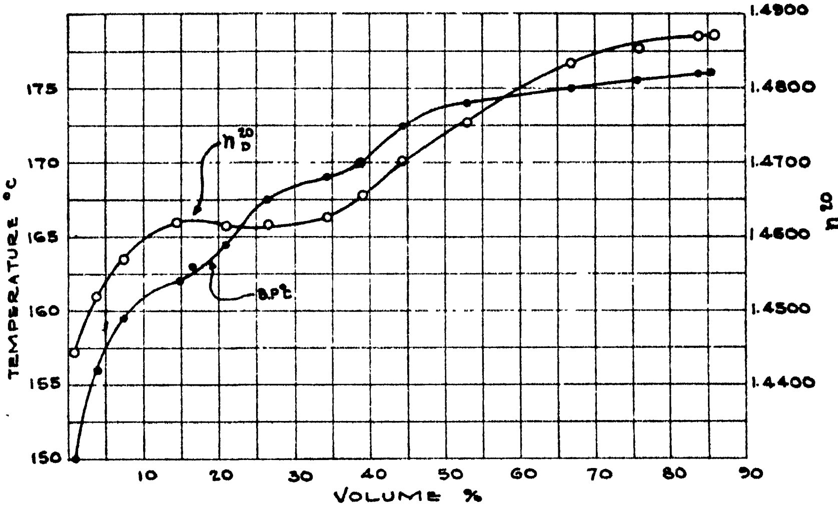
[4] Microanalyses were made by Dr. T. S. Ma, University of Chicago.

Anal. Calc'd for $C_{10}H_{18}$: C, 86.87; H, 13.13.
Found: C, 87.02; H, 12.76.

The higher-boiling hydrocarbons, boiling at 128–135°, at 4 mm., n_D^{20} 1.5222 consisted of product of reaction between benzene and the bicyclic terpene.

Fraction b.p. 164–167°, n_D^{20} 1.4613. Twenty-five grams of the product was treated with benzene in the presence of sulfuric acid. The upper layer contained 7 g. of hydrocarbons boiling at 166–168°, n_D^{20} 1.4665. This hydrocarbon after selective hydrogenation and removal of *p*-cymene, which was originally present, with fuming sulfuric acid distilled at 162–165°, n_D^{20} 1.4515 and consisted of bicyclic dihydroterpenes.

The product of the reaction of benzene with the bicyclic terpene distilled at 160–170° at 27 mm., n_D^{20} 1.5270, d_4^{20} 0.9555; it consisted of tricyclic hydrocarbons.



GRAPH II

Anal. Calc'd for $C_{16}H_{22}$: C, 89.65; H, 10.35.
Found: C, 89.45; H, 10.36.

Investigation of bicyclic dihydroterpene. In order to prepare a large amount of bicyclic dihydroterpenes, 2155 g. of monomeric fraction was selectively hydrogenated with a nickel-kieselguhr catalyst; by this method the olefinic hydrocarbons were converted into saturated product while *p*-cymene remained unchanged. After the extraction of *p*-cymene with fuming sulfuric acid, the *p*-menthane present was removed by an exhaustive dehydrogenation at 260° followed by extraction with fuming sulfuric acid; 839 g. of bicyclic dihydroterpenes was obtained which indicated that the original monomeric fraction contained 39.8% of bicyclic terpenes formed by cycloisomerization of limonene. The bicyclic dihydroterpenes were distilled on a column of an efficiency of fifty theoretical plates and at a reflux ratio 5:1. The distillation and the index refraction of the product is given in Graph III.

Some of the fractions were analyzed and the data are given in table on p. 40.

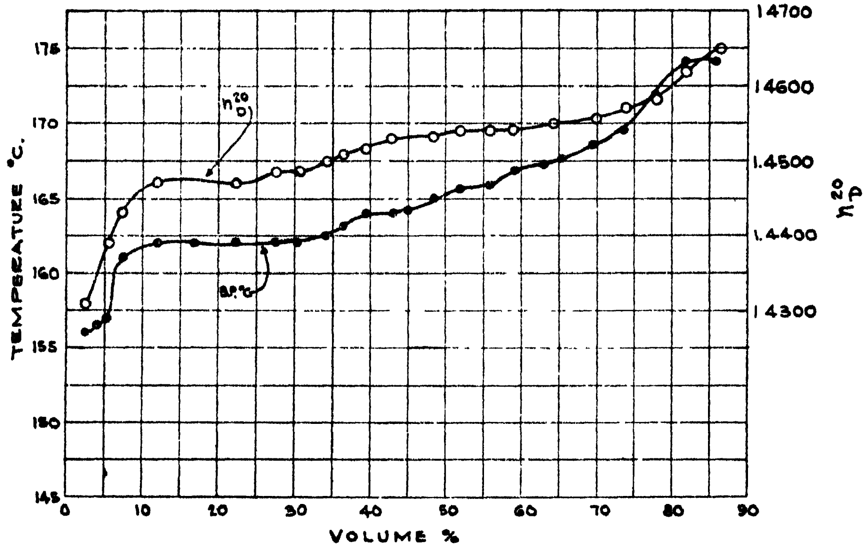
Treatment with aqueous magnesium chloride solution. Fifty-seven grams of the bicyclic dihydroterpenes, boiling at 164–166°, n_D^{20} 1.4527, was heated at 100° for two hours in a rotating autoclave of 850-ml. capacity with an equal volume of a 2% aqueous magnesium chloride solution. A very small amount of gas was liberated by the reaction. The hydrocarbon layer was separated, dried, and the resulting fifty-two grams was distilled. The material

FRACTION	B.P.	FOUND*		n_D^{20}
		C	H	
2	156	86.95	13.16	1.4389
5	162	86.76	12.95	1.4485
13	165	86.99	13.08	1.4539
17	167	86.95	13.16	1.4548
21	173	87.26	12.77	

* Calculated for $C_{10}H_{18}$: C, 86.87; H, 13.13.

remained unchanged as it distilled within the same range as the original product; its index of refraction after treatment was 1.4529.

Anal. Calc'd for $C_{10}H_{18}$: C, 86.87; H, 13.13.
Found: C, 87.03; H, 13.00.



GRAPH-III

Destructive hydrogenation. Two fractions of the bicyclic dihydroterpenes were subjected separately to destructive hydrogenation.

A. *Fraction b.p. 162°.* Thirty grams of the product was hydrogenated in an autoclave of a 450-ml. capacity with a nickel-kieselguhr catalyst and at an initial hydrogen pressure of 100 atmospheres. At 180–200° hydrogenation did not occur. By raising the temperature to 230° and maintaining the autoclave at this temperature for two hours, destructive hydrogenation took place; the final pressure at 25° was 80 atm. Thirty-two liters of gas was obtained composed of 63% hydrogen and 37% methane. It was calculated that 3.3 moles of hydrogen per mole of hydrocarbons charged entered into reaction. Twenty-two grams of liquid product was recovered which distilled as follows: (a) 50–75°, 7.3%; (b) 75–90°, 8.9%, n_D^{20} 1.3908; (c) 90–100°, 15.0%, n_D^{20} 1.4027; (d) 105–120°, 22.2%, n_D^{20} 1.4100; (e) 120–135°, 20.1%, n_D^{20} 1.4206; (f) 135–142°, 19.9%, n_D^{20} 1.4343.

Cut e obtained from the destructive hydrogenation was dehydrogenated by passing it over platinized alumina catalyst at 240°. One hundred fifty ml. of hydrogen was liberated; the liquid product obtained had n_{D}^{20} 1.4242, and it contained, according to absorption with 15% fuming sulfuric acid, 5% of aromatic hydrocarbons.

B. *Fraction b.p. 167°.* Thirty-three grams of the bicyclic dihydroterpenes was destructively hydrogenated at 230° under conditions described in A. Thirty liters of non-condensable gas was obtained which was composed of 55.4% hydrogen and 42.3% methane. Twenty-three grams of liquid hydrocarbon was recovered which distilled as follows: (a) 50–85°, 9%, n_{D}^{20} 1.3850; (b) 85–100°, 16%, n_{D}^{20} 1.4042; (c) 100–120°, 25% n_{D}^{20} 1.4138; (d) 120–136°, 23%, n_{D}^{20} 1.4223; (e) 136–148°, 25%, n_{D}^{20} 1.4367.

Cut c was dehydrogenated by passing it over platinized alumina at 250°. Three hundred eighty ml. of hydrogen was liberated. The liquid product, after the removal by fuming sulfuric acid of the 5% of aromatic formed, gave the following analysis.

Anal. Calc'd for C_7H_{14}: C, 85.63; H, 14.37.

Found: C, 86.12; H, 14.22.

These data show that Fraction c consisted of hydrocarbons containing mainly a pentamethylenic ring, with some alkylcyclohexanes.

Cut d analyzed as follows:

Anal. Calc'd for C_8H_{16}: C, 85.63; H, 14.37.

Found: C, 86.65; H, 14.11.

Four and one-half grams of the product was dehydrogenated by passing it over platinized alumina three times at 240°. One thousand twenty ml. of hydrogen was liberated. A liquid product distilling at 130–136°, n_{D}^{20} 1.4360, was obtained; according to ultraviolet absorption analysis it contained 11.7% of *o*-xylene; 5.1% of *m*-xylene, and 1.9% of *p*-xylene.[5] No ethylbenzene was present.

A nitro derivative was prepared melting at 174° corresponding to dinitro-*m*-xylene.

Dehydrogenation. Twenty grams of bicyclic dihydroterpenes, b.p. 163°, n_{D}^{20} 1.4530 was passed over platinized alumina at 300° with an hourly liquid space velocity of 0.1. Two hundred forty ml. of gas was formed, the index of refraction of the resulting liquid product was 1 4558; it showed a positive test for aromatics and a negative test for olefins. In order to separate the aromatic hydrocarbons, the product was passed over silica-gel according to the procedure described by Mair and Forziati (8). Two and one-half ml. of aromatic hydrocarbons, n_{D}^{20} 1.4900, was separated which, according to infrared analysis, consisted of *p*-cymene.

The action of liquid phosphoric acid on limonene. Three hundred thirty-seven grams of *d*-limonene was stirred with 360 g of 85% phosphoric acid at room temperature for 128 hours. The upper layer was steam distilled in the presence of sodium hydroxide, dried, and fractionally distilled. Forty-eight ml. of hydrocarbons distilling at 166–175° was obtained, which did not contain any diolefins as determined by benzene-sulfuric acid color test. A part of the hydrocarbons was selectively hydrogenated at 45° using nickel-kieselguhr catalyst to saturate the olefin. According to ultraviolet absorption, the product contained 22% of *p*-cymene. This was removed from the saturated hydrocarbons by extraction with fuming sulfuric acid. The aromatic-free hydrocarbons distilled at 166–168°, n_{D}^{20} 1.4395. On dehydrogenation, *p*-cymene was obtained.

Acknowledgment. The authors are indebted to Drs. M. J. Murray and W. S. Gallaway of the Universal Oil Products Company for the ultraviolet and infrared analyses, respectively.

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[5] The presence of the various isomeric xylenes in the dehydrogenation product is not an indication that the corresponding dimethylcyclohexanes were present in the product of the destructive hydrogenation, inasmuch as xylenes may probably undergo isomerization when passed over platinized alumina.

SUMMARY

By passing *d*-limonene over silicophosphoric acid at 200°, a mixture of hydrocarbons was obtained consisting of 55% of polymers and 45% of monomers.

The monomeric fraction consisted of bicyclic terpenes, monocyclic dihydroterpenes and *p*-cymene.

The probable structure for the bicyclic terpenes, resulting from the cyclic isomerization of limonene is given as 2,6-dimethyl-bicyclo-(3,2,1)-2-octene; this conclusion being based upon the evidence obtained by degradative oxidation, destructive hydrogenation, treatment with dilute acid-acting salts, and dehydrogenation.

EVANSTON, ILL.

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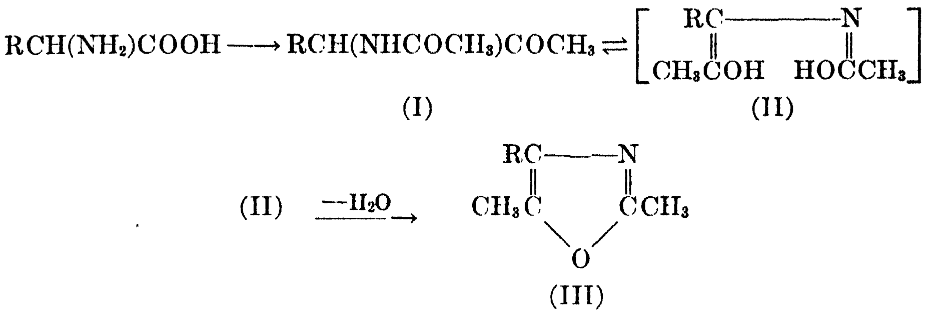
[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

THE CONVERSION OF α-AMINO ACIDS TO OXAZOLES

RICHARD H. WILEY

Received April 16, 1946

This investigation was undertaken to substantiate a proposed mechanism (1) for the conversion of α-amino acids to oxazoles. In this proposed mechanism it was suggested that the α-amino acid was first converted to an acylamido ketone (I) which was then dehydrated, through the hypothetical enol form (II), to the 2,5-dimethyl-4-substituted oxazole (III).



$RCH(NH_2)COOH \longrightarrow RCH(NHCOCH_3)COCH_3 \rightleftharpoons \left[\begin{array}{ccc} RC & \text{———} & N \\ \| & & \| \\ CH_3COH & & HOCCH_3 \end{array}\right]$

(I) (II)

$(II) \xrightarrow{-H_2O}$

(III)

Conclusions drawn from the work of Levene and Steiger (2) and Dakin and West (3) indicated that conversion of the amino acid to the ketone (I) should take place readily. The work by Robinson and his co-workers (4) and by Gabriel (5) suggested the feasibility of the conversion of the ketone (II) to the oxazole (III).

In accordance with this mechanism three amino acids—alanine, leucine, and phenylaminoacetic acid—have been converted to oxazoles through the corresponding acetamido ketones. The acetamido ketones, two of which had been prepared previously but not isolated (3), were isolated for more complete characterization. The oxazoles were prepared from these ketones by dehydration with sulfuric acid. Over-all yields were 15.6% of 2,4,5-trimethyloxazole from alanine, 58.5% of 2,5-dimethyl-4-isobutyloxazole from leucine, and 53.5% of 2,5-dimethyl-4-phenyloxazole from phenylaminoacetic acid. The yields with the last two are an improvement over the yields obtained by the acetic anhydride-sodium acetate-phosphorus pentachloride method (6) for converting α-amino acids to oxazoles. The low yield from alanine is attributed to loss through hydrolysis during the steam distillation purification of the acetamido ketone and to difficulties encountered in working with the highly volatile trimethyloxazole (6). Investigation of alternative methods for conducting these reactions in better yields is in progress. It is believed, however, that the successful completion of the reactions provides support for the proposed mechanism.

The molecular refractivities of the compounds described in this study are presented in the table. Additional molecular refractivity data on the oxazoles have been reported by Auwers and Ernst (7), who observed depressions of 1.24 and 1.72 for 2,4- and 2,5-dimethyloxazoles and of 0.06 for 4-phenyloxazole, and exaltations of 0.63 and 2.62 for 5-phenyl- and 2,5-diphenyl-oxazole. These variations from the calculated values are in accord with the variations reported here. Thus the depressions with 2,4,5-trimethyl- and 2,5-dimethyl-4-isobutyloxazoles are 1.26 and 1.13, while the 2,5-dimethyl-4-phenyloxazole shows a slight (+0.12) exaltation. It may be noted that the variation in the observed refractivities of the four aliphatically substituted oxazoles is less than the variation in the value of N in C—N=C used to determine the calculated values in the table. This raises a question as to absolute accuracy of these calculated values and as to the significance of the deviations. If, however, the depressions are real, then the oxazoles are similar to other conjugated cyclic compounds which show such depressions (11).

TABLE I

MOLECULAR REFRACTIVITIES

COMPOUND	MOLECULAR REFRACTIVITY		EXALTATION OR DEPRESSION	VALUE FOR C=N
	Obs'd	Calc'd		
II, R is CH_3	33.72	33.31[a] 33.55[b]	+0.41[a] +0.17[b]	
II, R is i-C_4H_9	47.65	47.17[a] 47.41[b]	+0.48[a] +0.21[b]	
I, R is CH_3	30.63	31.89[c] 27.67[d]	−1.26[c]	2.96
I, R is i-C_4H_9	44.62	45.75[c] 41.62[d]	−1.13[c]	3.00
I, R is C_6H_5	51.50	51.38[c] 47.45[d]	+0.12[c]	4.05

[a] Using atomic values given in Shriner and Fuson (8).
[b] Using bond values given by Denbigh (9).
[c] Using the value of 4.10 for N in C—N=C given by Auwers and Ottens (10).
[d] Using aliphatic bond values with no value added for the C=N.
[e] In the oxazole ring.

The calculations of molecular refractivities are given in the table in terms of the bond values assigned by Denbigh (9), who has, however, reported no value for the carbon to nitrogen double bond. These calculated values, made without inclusion of a value for the carbon to nitrogen double bond, have been used to determine a value for this double bond in the oxazole ring by subtracting from the observed value. Compared to the value of 2.96 to 3.00, the 4-phenyl derivative shows an exaltation of 1.05 to 1.09. Such an exaltation is probably associated with the increased conjugation and resonance possibilities. The fluorescence of the 2,5-dimethyl-4-phenyloxazole and the other aromatically substituted oxazoles is probably another manifestation of this phenomenon.

EXPERIMENTAL PART

All melting points are corrected.

3-Acetamidobutanone-2 (II, R = CH_3). Seventy-five grams of alanine (dec. pt. 295°), 340 ml. of pyridine, and 340 ml. of acetic anhydride were heated on the steam-bath. At the end of six hours the reaction solution was steam distilled to decompose the acetic anhydride and to remove acetic acid and pyridine. After one hour the condensate was neutral to litmus. The residue in the distilling flask was reduced to a volume of 150 ml. by external heating during the steam distillation This residue was extracted with ether in a continuous extractor (12) for several days to extract the acetamido ketone. The extraction was slow because of the very low solubility of the ketone in ether. The crude extract was freed of ether and fractionated to give 49.8 g. or 45.8% of 3-acetamidobutanone-2, b.p. 104–110° at 2–3 mm. A center cut from this fraction, b.p. 105.5–107° at 2 mm., d_{25}^{25} 1.040, n_D^{25} 1.4561, was analyzed.

Anal. Calc'd for $C_6H_{11}NO_2$: N, 10.85. Found. N, 10.90.

This procedure using ether for the extraction gave better yields of isolated product than did the procedure using butanol for the extraction (4), but neither is entirely satisfactory.

3-Acetamido-5-methylhexanone-2 [II, R = $(CH_3)_2CHCH_2$]. Fifty grams of *l*-leucine (E. K. Co.), 167 ml. of pyridine, and 167 ml. of acetic anhydride were heated on the steam-bath for six hours. The solution formed in this reaction was steam distilled as in the preceding example. When the volume of the liquid in the distilling flask was reduced to 200–300 ml., an oil separated. The contents of the distilling flask were extracted with ether, the ether extracts combined, dried, and distilled. The residue was fractionated to give 46 1 g., or 70.7% of 3 acetamido-5 methylhexanone 2, b p 122–134° at 2–3 mm., n_D^{25} 1.4555, d_{25}^{25}0.975.

Anal. Calc'd for $C_9H_{17}NO_2$: N, 8.19. Found: N, 8.04.

1-Acetamido-1-phenylpropanone-2 (II, R = C_6H_5). Ninety grams of phenylaminoacetic acid (E K. Co.), 300 g. of pyridine, and 450 g. of acetic anhydride were heated on the steam-bath for 5.5 hours. The reaction solution was steam distilled as in the preceding examples. The contents of the distilling flask were extracted with ether. On evaporating the ether, 110 g., 96.5% of solidified 1-acetamido-1-phenylpropanone-2 was obtained. On recrystallization from 300 ml of xylene, 60.5 g. of product, m.p. 98- 100°, was obtained. On evaporating the mother liquors, 12.2 g. of solid was obtained in the second crop of crystals; yield 72.7%. A second crystallization from xylene gave a solid, m.p. 99.5–100.5°; a third did not raise the m p [m.p. reported 103–104° (6)].

Anal. Calc'd for $C_{11}H_{13}NO_2$: N, 7.33. Found: N, 7.45.

2,4,5-Trimethyloxazole (I, R = CH_3). Thirty grams of 3-acetamidobutanone-2 was dissolved in 100 ml. of concentrated sulfuric acid with cooling. This solution was heated on the water-bath for 0.5 hour and then poured with stirring onto 500 ml. of crushed ice. The free oxazole was liberated from this acid solution by adding 155 g. of sodium hydroxide in 200 ml of water. During the addition the temperature was held at 20–25°. The oxazole, which separated as an oil, was collected, dried, and distilled to give 15 g. of an unidentified low-boiling fraction, and 9.0 g., or 34.8% of 2,4,5-trimethyloxazole. On refractionation, 4.0 g. of a fraction, b p. 132–133° [reported b p. 134° (6)], d_{25}^{25} 0.9566, n_D^{25} 1.4413, was separated and analyzed.

Anal. Calc'd for C_6H_9NO: N, 12.61. Found: N, 12.62.

The picrate of 2,4,5-trimethyloxazole was prepared by adding a warm solution of 1.15 g. of picric acid in 20 ml. of 95% alcohol to a solution of 0.55 g. of the oxazole in 10 ml. of 95% alcohol. On standing, large crystals of 2,4,5-trimethyloxazole picrate separated These were washed with ether, and dried in a desiccator over phosphorus pentoxide; m.p. 110.5–112.5° [reported m p. 115° (6)]. Repeated recrystallization did not alter this m.p.

Anal. Calc'd for $C_{12}H_{12}N_4O_8$: N, 16.47. Found: N, 16.40.

2,5-Dimethyl-4-isobutyloxazole [I, R. = $(CH_2)_2CHCH_2$]. Forty grams of 3-acetamido-5-methylhexanone-2 was dissolved in 200 ml. of concentrated sulfuric acid and heated one hour on the steam-bath. This solution was poured onto one l. of crushed ice and neutralized by adding solid sodium carbonate. The neutralized solution was extracted with ether. On fractionation of the residue, 29.4 g., or 82.6% of 2,5-dimethyl-4-isobutyloxazole, b.p. 171–185° [reported b.p. 180° (6)] was separated. On refractionation 17.0 g., b.p. 176–177°, d_{25}^{25} 0.9126, n_D^{25} 1.4450, was separated.

Anal. Calc'd for $C_9H_{15}NO$: N, 9.15. Found: N, 9.22.

2,5-Dimethyl-4-isobutyloxazole picrate was prepared by adding a hot solution of 2.29 g. of picric acid in 10 ml. of 95% alcohol to a solution of 1.53 g. of the oxazole in six ml. of 95% alcohol. The crystals were washed with alcohol and dried; m.p. 90.5–91° [reported m.p. 92° (6)]. Repeated recrystallization from alcohol did not raise this m.p.

Anal. Calc'd for $C_{15}H_{18}N_4O_8$. N, 14.66. Found: N, 14.56.

2,5-Dimethyl-4-phenyloxazole (I, R = C_6H_5). This oxazole was prepared from 50 g. of 1-acetamido 1-phenylpropanone-2 in 200 ml of concentrated sulfuric acid in the manner described above for the preparation of the 4-isobutyl derivative. Thirty-seven and eight-tenths grams, or 83.5% of 2,5-dimethyl-4-phenyloxazole, b.p. 249–263°, was collected and refractionated to give 34 g. of the oxazole, b.p. 255–258°, d_{25}^{25} 1.088, n_D^{25} 1.5613. A solution of this oxazole in concentrated sulfuric acid is violet colored and appears greenish-yellow when exposed to ultraviolet light. Its ethanol solution is faintly violet.

Anal. Calc'd for $C_{11}H_{11}NO$: N, 8.09. Found. N, 7.96.

2,5-Dimethyl-4-phenyloxazole picrate was prepared, in the manner described for the preparation of the picrate of the 4-isobutyl derivative; the m p. 129.5–130.5° was not raised by repeated crystallization from alcohol.

Anal. Calc'd for $C_{17}H_{14}N_4O_8$: N, 13.93. Found: N, 13.92.

SUMMARY

A new method for converting α-amino acids to oxazoles has been developed from a proposed mechanism for the reaction. Alanine, leucine, and phenylaminoacetic acid have been converted to 3-acetamidobutanone-2 (II, R is CH_3), 3-acetamido-5-methylhexanone-2 (II, R is i-C_4H_9), and 1-acetamido-1-phenylpropanone-2 (II, R is C_6H_5), respectively, by reaction with acetic anhydride and pyridine. These acetamido ketones have been converted in turn to 2,4,5-trimethyloxazole, 2,5-dimethyl-4-isobutyloxazole, and 2,5-dimethyl-4-phenyloxazole by heating in concentrated sulfuric acid in over-all yields of 15.6 to 58.5%. The molecular refractivities of the oxazoles have been observed and deviations similar to those previously reported have been confirmed.

Chapel Hill, N. C.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

CINNOLINES. III. ATTEMPTED SYNTHESES OF THE CINNOLINE NUCLEUS[1]

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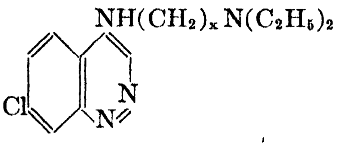
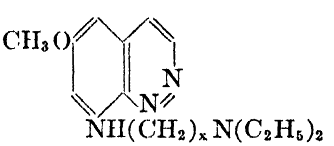
In the search for efficient methods of preparing potential antimalarial drugs (1, 2) of the 7-chloro-4-dialkylaminoalkylaminocinnoline (I) and 8-dialkylaminoalkylamino-6-methoxycinnoline (II) types, new methods of synthesis of the cinnoline nucleus were attempted.



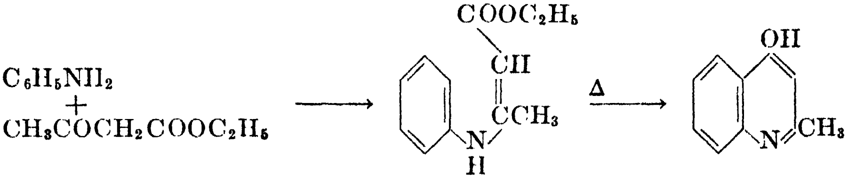
I



II

The limitations of existing methods have been reported recently (3). The development of new methods of ring closure for the cinnolines based upon cyclization procedures applied to the quinoline series appeared worthy of investigation. The results obtained indicate that in at least four different general types of ring closure, cinnolines were not formed from intermediates which were exact analogs of the precursors of quinolines.

Method A. Conrad and Limpach (4) found that aniline could be condensed with acetoacetic ester to form ethyl β-anilinocrotonate (III), which could be cyclized by various methods to form 4-hydroxyquinaldine (IV).



III IV

The same authors extended the reaction to other amines and other carbonyl compounds. In this laboratory, the scope of the reaction has been expanded

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[1] The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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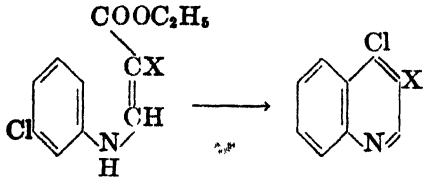
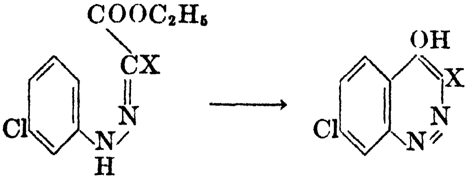
(V → VI) and it has been applied particularly to the synthesis of 7-chloro-4-hydroxyquinoline, intermediate in the preparation of 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (5).



V VI

(X = CN, $COCH_3$, $COOC_2H_5$, $CONHC_6H_5Cl$-*m*, H, CH_3)

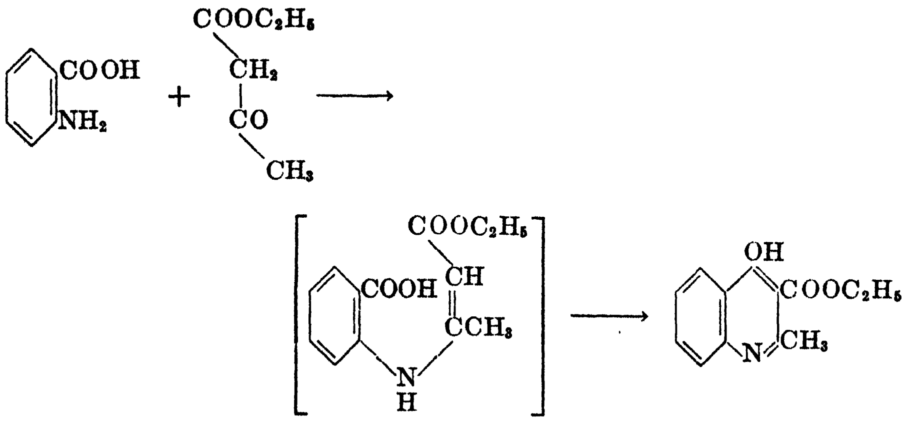


VII VIII

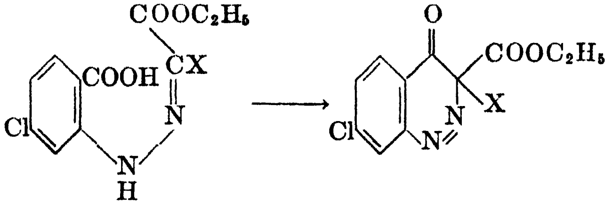
(X = CN, $COCH_3$, $COOC_2H_5$)

Similar treatment of *m*-chlorophenylhydrazones (VII) analogous to V might be expected to produce 7-chloro-4-hydroxycinnolines substituted in the 3-position (VIII). Accordingly, ethyl cyanoglyoxylate *m*-chlorophenylhydrazone (VII, X = CN), ethyl α,β-diketobutyrate α-*m*-chlorophenylhydrazone (VII, X = $COCH_3$), and diethyl mesoxalate *m*-chlorophenylhydrazone (VII, X = $COOC_2H_5$) were prepared by coupling diazotized *m*-chloroaniline with cyanoacetic ester, acetoacetic ester, and malonic ester, respectively. In an approach to compound II, diethyl mesoxalate 4-methoxy-2-nitrophenylhydrazone was prepared by coupling 4-methoxy-2-nitrobenzenediazonium chloride with malonic ester. No cinnoline formation was observed when these substituted phenylhydrazones were heated in an inert solvent. A wide range of temperature and length of heating time was employed; however, when extensive decomposition did not occur, only starting material was isolated. Since the predominating evidence favors the phenylhydrazone type of structure for these compounds rather than the tautomeric azo form (6), the coupling products are named on the basis of phenylhydrazones although no new evidence as to structure is presented at this time.

Method B. The second attempted cinnoline synthesis was suggested by the work of von Niementowski (7), who prepared substituted 4-hydroxyquinolines (IX) by the condensation of a carbonyl compound, such as acetoacetic ester, with an anthranilic acid. Thermal treatment of analogous 2-carboxy-5-chlorophenylhydrazones (X) might be expected to produce substituted 7-chlorocinnolines (XI).



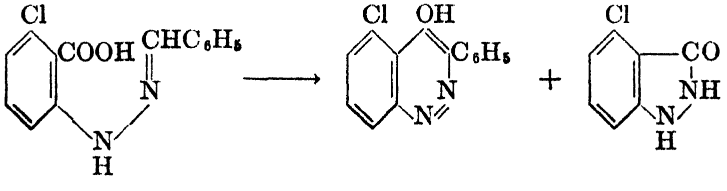
IX



X XI

(X = $COOC_2H_5$, $COCH_3$, H)

This method would be similar to that employed by Pfannstiel and Janecke (8), who heated benzaldehyde 2-carboxy-3-chlorophenylhydrazone (XII) to obtain 5-chloro-4-hydroxy-3-phenylcinnoline (XIII) in low yield, along with 4-chloroindazolone (XIV).

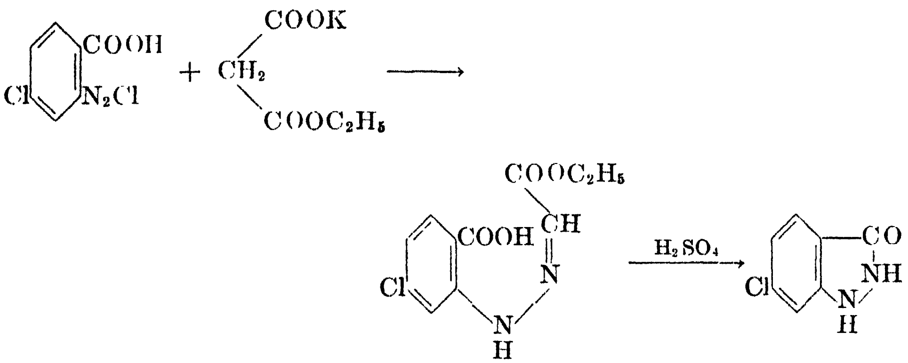


XII XIII XIV

Diethyl mesoxalate 2-carboxy-5-chlorophenylhydrazone (X, X = $COOC_2H_5$) and ethyl α,β-diketobutyrate α-2-carboxy-5-chlorophenylhydrazone (X, X = $COCH_3$) were prepared by coupling diazotized 2-amino-4-chlorobenzoic acid with malonic ester and acetoacetic ester. Neither compound could be induced to undergo cinnoline ring closure under thermal or acid treatment.

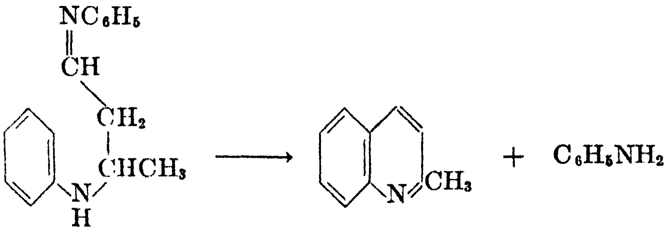
Ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone (X, X = H) was prepared by coupling diazotized 2-amino-4-chlorobenzoic acid with the monopotassium salt of ethyl hydrogen malonate. Ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone was prepared in similar manner from diazotized 2-amino-5-chlorobenzoic acid. Diazotized 2-amino-3,5-diiodobenzoic acid behaved anomalously when treated with ethyl hydrogen malonate. The product isolated had the composition of 3,5-diiodobenzoic acid, and the melting point agreed with that reported by Wheeler and Liddle (9) for this diiodobenzoic acid.

When ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone and 2-carboxy-4-chlorophenylhydrazone were treated with concentrated sulfuric acid, cyclization occurred, but the products were not cinnolines. That 6-chloroindazolone (XV) and 5-chloroindazolone were the products of ring closure is indicated by the analytical data and is inferred from the course of the analogous cyclization by Pfannstiel and Janecke (8). These chloroindazolones have not been reported previously. Thermal treatment of ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone and 2-carboxy-4-chlorophenylhydrazone was ineffective in causing cyclization.



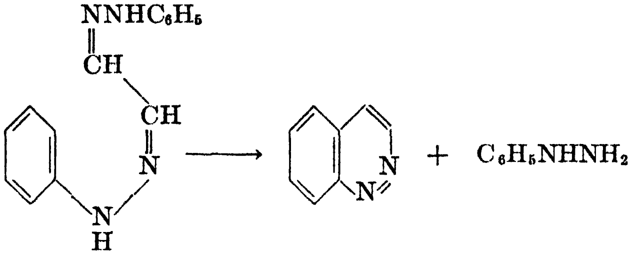
XV

Method C. Evidence that ring closure in the Skraup reaction proceeds through elimination of a mole of aniline from the anil XVI (10) is found in the formation of quinaldine (XVII) rather than lepidine when crotonaldehyde is condensed with aniline.



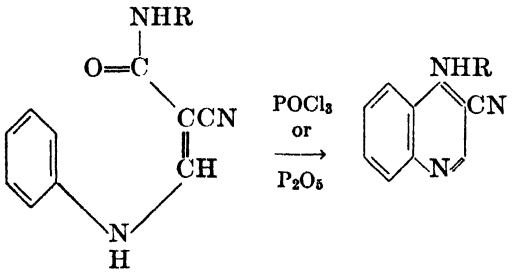
XVI XVII

In order that a cinnoline be obtained through a reaction of this sort, it was proposed that glyoxal phenylosazone (XVIII) be used as the intermediate. Ring closure in this case would lead directly to cinnoline (XIX) and, if successful, the reaction could be extended to appropriately substituted phenylosazones of glyoxal. The ring closures attempted with various acidic catalysts were uniformly unsuccessful. From the reactions using sulfuric acid, hydrochloric acid, and boron trifluoride diethyl etherate, the only product recovered was phenylhydrazine, identified through its explosive picrate. Only a small quantity of aniline was isolated as the picrate from the reaction of glyoxal phenylosazone with zinc chloride and hydrogen chloride in ethanol.

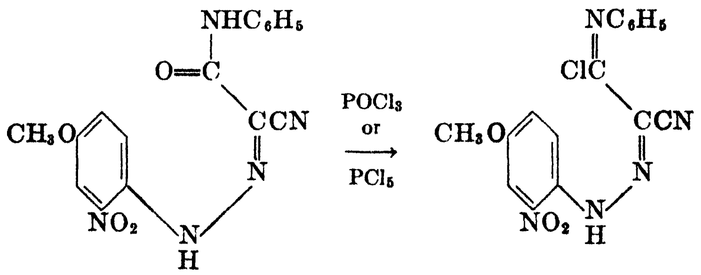


XVIII XIX

Method D. The ring closure of β-anilinoacrylamides (XX) with either phosphorus oxychloride or phosphorus pentoxide has been developed recently by Price and Boekelheide (11) as a route to the 4-aminoquinolines (XXI). α-Cyanoglyoxanilide 4-methoxy-2-nitrophenylhydrazone (XXII) was prepared readily by coupling diazotized 2-nitro-*p*-anisidine with cyanoacetanilide.



XX XXI



XXII XXIII

The attempted cyclization in benzene with phosphorus pentoxide under conditions which had been used for the preparation of the aminoquinolines furnished only tars from which about half of the unchanged amide was recovered. From refluxing phosphorus oxychloride or from refluxing benzene and phosphorus pentachloride, only the imidochloride (XXIII) could be isolated in good yield. Shah and Ichaporia (12) found that a Friedel-Crafts condensation of benzanilide imidochloride with dimethylaniline could be effected by the use of one mole of aluminum chloride. In an attempted ring closure of the 4-methoxy-2-nitrophenylhydrazone of cyanoglyoxanilide imidochloride (XXIII) with one and one-quarter moles of aluminum chloride in carbon disulfide, the imidochloride was recovered unchanged. With three moles of aluminum chloride in nitrobenzene at 73°, the imidochloride gave only resinous products.

EXPERIMENTAL[4]

Method A. m-Chlorobenzenediazonium chloride m-Chloroaniline (114 g., 0.90 mole) was diazotized in the usual manner with nitrous acid in hydrochloric acid solution. Darco was added to the diazonium salt solution, which was stirred for ten minutes below 10° and filtered. The filtrate was divided into three equal portions.

Ethyl cyanoglyoxylate m-chlorophenylhydrazone One-third of the above *m*-chlorobenzenediazonium chloride solution was added dropwise over a period of one hour to a well-stirred mixture of 33.9 g (0.30 mole) of cyanoacetic ester in 300 cc. of water at 5–10°. Sodium carbonate (100 g) was added in small portions to keep the reaction mixture alkaline to litmus. The reaction mixture was extracted with ether until the ether layer was no longer colored. The ether extracts were combined and dried over magnesium sulfate. The residue was recrystallized from ethanol as pale orange crystals, m.p. 89–90°, in a yield of 73 g. (97%). A sample recrystallized from ethanol for analysis melted at 91°.

Anal. Calc'd for $C_{11}H_{10}ClN_3O_2$: C, 52.49; H, 4.01.
Found: C, 52.49; H, 4.03

Ethyl α,β-diketobutyrate α-m-chlorophenylhydrazone. This compound was prepared and isolated in the same manner as ethyl cyanoglyoxylate *m*-chlorophenylhydrazone Thirty-nine grams (0.30 mole) of acetoacetic ester was substituted for the cyanoacetic ester. After recrystallization from ethanol, the compound formed fine yellow needles which melted at 86°. The yield was 63 g. (78.2%).

Anal. Calc'd for $C_{12}H_{13}ClN_2O_3$: C, 53.63; H, 4.88.
Found: C, 53.54; H, 4.85.

Diethyl mesoxalate m-chlorophenylhydrazone. This compound was prepared from 48 g. (0.30 mole) of malonic ester and isolated in the same manner as the above two *m*-chlorophenylhydrazones. Seventy grams (78.2%) of pale orange crystals was obtained, which melted at 56° after recrystallization from ethanol.

Anal. Calc'd for $C_{13}H_{15}ClN_2O_4$: C, 52.27; H, 5.06.
Found: C, 52.31; H, 5.20.

4-Methoxy-2-nitrobenzenediazonium chloride. A hot solution of 16.8 g. (0.1 mole) of 2-nitro-*p*-anisidine in 30 cc. of water and 21 cc. of concentrated hydrochloric acid was poured onto 30 g. of ice and cooled to 0–5°. An aqueous solution of 7.0 g. (0.1 mole) of sodium nitrite was added at once with vigorous stirring. After ten minutes the excess nitrous acid was destroyed with sulfamic acid and the solution was filtered.

Diethyl mesoxalate 4-methoxy-2-nitrophenylhydrazone. One-half of the above 4-methoxy-

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[4] All melting points, unless otherwise specified, are corrected for both emergent stem and thermometer errors. Boiling points are not corrected. Microanalyses were performed by Miss Theta Spoor, Miss Lillian Hruda, and Mr Howard Clark.

2-nitrobenzenediazonium chloride solution was added slowly with stirring to a solution of 8.0 g. (0.05 mole) of diethyl malonate and 7.0 g. of sodium acetate in 155 cc. of ethanol and 20 cc. of water. After an hour at ice-bath temperature, the suspension was allowed to come to room temperature and to stand overnight. After addition to 800 cc. of water, the coupled product was removed by filtration. The hydrazone crystallized as lustrous orange needles from benzene-petroleum ether or ethanol; m.p. 132–132.5°; yield, 8.0 g. (47%).

Anal. Calc'd for $C_{14}H_{17}N_3O_7$: C, 49.56; H, 5.05.
Found: C, 49.94; H, 5.28.

The conditions employed for the unsuccessful thermal cyclization are summarized in Table I.

Method B. Diazotization of 2-amino-4-chlorobenzoic acid. 2-Amino-4-chlorobenzoic acid (10.9 g., 0.063 mole) was dissolved in 40 cc. of 2 *N* sodium hydroxide, and 12.7 cc. of a 5 *N* solution of sodium nitrite was added. The resulting solution was mixed thoroughly and added dropwise to a well-stirred mixture of 38 cc. of concentrated hydrochloric acid and 200 cc. of crushed ice. The system was immersed in an ice-salt bath, and the addition was carried out at such a rate that the temperature of the reaction mixture did not exceed 8°. The mixture was stirred for an additional hour below 8°. The excess nitrous acid was destroyed by the addition of urea, and the diazonium solution was divided into three equal parts.

TABLE I

ATTEMPTED CYCLIZATION OF SUBSTITUTED PHENYLHYDRAZONES

METHOD A

COMPOUND	AMOUNT, G	SOLVENT	AMOUNT, CC.	TEMP.	TIME, HRS.
Ethyl cyanoglyoxylate *m*-chlorophenylhydrazone	15	$(C_6H_5)_2O$	500	Reflux	11[a,b]
Ethyl α,β-diketobutyrate α-*m*-chlorophenylhydrazone	10	$(C_6H_5)_2O$	50	230–240°	4
	15	$(C_6H_5)_2O$	500	Reflux	5[a]
Diethyl mesoxalate *m*-chlorophenylhydrazone	15	$(C_6H_5)_2O$	500	Reflux	11[a,b]
	15	*p*-Cymene	100	Reflux	21[a]
	10	Toluene	100	Reflux	42
	10	Tetralin	100	Reflux	22
Diethyl mesoxalate 4-methoxy-2-nitrophenylhydrazone	6	$(C_6H_5)_2O$	50	Reflux	3[a]

[a] Nitrogen stream bubbled through solution.

[b] The diphenyl ether solution was refluxed with aqueous 16% sodium hydroxide for 3 hrs. The aqueous layer was separated and rendered acid with hydrochloric acid. No precipitate resulted.

Diethyl mesoxalate 2-carboxy-5-chlorophenylhydrazone. One portion of the diazonium salt solution, which was prepared as described above, was added to a well-stirred mixture of 7 g. of malonic ester and 40 cc. of a saturated aqueous solution of sodium acetate. The mixture was stirred in an ice-bath for one and one-half hours and was then allowed to stand overnight at room temperature. The mixture was made strongly acid with concentrated hydrochloric acid. The precipitate was removed by filtration and washed with water until free from acid. The yield was 4.8 g. (67%) of fine white threads; m.p. 162–163°. A sample recyrstallized from ethanol for analysis melted at 163–164°.

Anal. Calc'd for $C_{14}H_{15}ClN_2O_6$: C, 49.06; H, 4.41; N, 8.18.
Found: C, 48.86; H, 4.69; N, 8.05.

Ethyl α,β-diketobutyrate α-2-carboxy-5-chlorophenylhydrazone. This compound was prepared in the same manner, with the substitution of 6.0 g. of acetoacetic ester for the malonic ester. The product formed yellow threads, m.p. 228–229°, after recrystallization from ethanol; yield, 4.4 g. (67%).

Anal. Calc'd for $C_{13}H_{13}ClN_2O_5$: C, 49.93; H, 4.19; N, 8.96.
Found: C, 50.01; H, 4.34; N, 8.95.

Ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone. This compound was prepared in the same manner as diethyl mesoxalate 2-carboxy-5-chlorophenylhydrazone. Seven grams of the monopotassium salt of ethyl hydrogen malonate, prepared by the method of Breslow, Baumgarten, and Hauser (13), was used in place of the malonic ester. The product separated as fine, white threads from ethanol; m.p 212–213°; yield, 4.1 g. (72%).

Anal. Calc'd for $C_{11}H_{11}ClN_2O_4$: C, 48.81; H, 4.10; N, 10.35.
Found: C, 49.03; H, 4.02; N, 10.47.

Ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone. Eight and six-tenths grams (0.05 mole) of 2-amino-5-chlorobenzoic acid (Eastman, technical grade) was diazotized in the same manner as 2-amino-4-chlorobenzoic acid. The diazonium salt solution was added to a cold solution of 13.0 g. of the monopotassium salt of ethyl hydrogen malonate and 13.0 g. of sodium acetate in 150 cc. of water, and the resulting mixture was stirred overnight. The reaction mixture was rendered distinctly acid by the addition of concentrated hydrochloric acid. The precipitate was removed by filtration and washed with water until free from acid. The product was recrystallized from ethanol as fine, white threads; m.p. 207–208°; yield, 7.0 g. (52%).

Anal. Calc'd for $C_{11}H_{11}ClN_2O_4$: C, 48.81; H, 4.10; N, 10.35.
Found: C, 49.06; H, 4.28; N, 10.36.

Attempted preparation of ethyl glyoxylate 2-carboxy-4,6-diiodophenylhydrazone. 3,5-Diiodobenzoic acid. To a solution of 19.5 g. (0.05 mole) of 2-amino-3,5-diiodobenzoic acid and 2.3 g. of sodium hydroxide in 230 cc. of water was added 10 cc of a 5 *N* solution of sodium nitrite. The solution was kept warm to prevent precipitation of any solid and was added dropwise over a period of thirty minutes to a well-stirred mixture of 23 cc. of concentrated hydrochloric acid and ice. The temperature of the reaction mixture was maintained below 15° by an ice-salt bath. An excess of nitrous acid was maintained for one hour and then destroyed by the addition of urea. The diazonium solution was added to a cold solution of 13 g. of the monopotassium salt of ethyl hydrogen malonate and 13 g. of sodium acetate in 150 cc. of water. The reaction mixture was stirred overnight and then rendered strongly acid by the addition of hydrochloric acid The precipitate was removed by filtration and washed with water until free from acid. After two recrystallizations from a mixture of ethanol, benzene, and petroleum ether (b.p. 90–110°), the product melted at 238° (uncor.) or 246° (cor.). The composition of the compound was suggestive of 3,5-diiodobenzoic acid, for which Wheeler and Liddle (9) have reported the melting point 235–236°. The yield was 9.0 g. (48%).

Anal. Calc'd for $C_7H_4I_2O_2$: C, 22.48; H, 1.08.
Found: C, 22.67; H, 1.38.

Action of sulfuric acid on the 2-carboxy-5-chloro- and 2-carboxy-4-chlorophenylhydrazones of ethyl glyoxylate. 6-Chloroindazolone. One gram of ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone was dissolved in 50 cc. of concentrated sulfuric acid. The resulting clear yellow solution was allowed to stand four hours at 25° and then poured onto ice. The clear aqueous solution was neutralized with ammonium hydroxide and cooled in an ice-bath. The fine, white crystals (*ca.* 0.5 g.) which separated were recrystallized from ethanol, m.p. 289°.

Anal. Calc'd for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.62.
Found: C, 49.87; H, 3.12; N, 16.31.

5-Chloroindazolone This compound was obtained when ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone (1 g.) was treated in the same manner as is reported above. About 0.5 g. of fine, white needles, m.p. 275–276°, was obtained after recrystallization from ethanol.

Anal. Calc'd for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.62.
Found: C, 49.78; H, 3.03; N, 16.68.

Method D. α-Cyanoglyoxanilide 4-methoxy-2-nitrophenylhydrazone. A solution of 4-methoxy-2-nitrobenzenediazonium chloride from 33.6 g. (0.2 mole) of 2-nitro-*p*-anisidine was added slowly to 32 g. (0.2 mole) of cyanoacetanilide (14) in 1 liter of ethanol to which a saturated aqueous solution of 45 g. of sodium acetate had been added previously. The product of the coupling was removed by filtration, recrystallized from pyridine, and digested with acetone to remove some of the color; yield, 38.5 g. (57%). Recrystallized from nitromethane and decolorized with activated charcoal, the compound was obtained as fine orange needles; m.p. 221–221.5°.

TABLE II

ATTEMPTED CYCLIZATION OF SUBSTITUTED PHENYLHYDRAZONES

METHODS B, C, D

REACTANTS	SOLVENT	TIME, HRS.	TEMP., °C	PRODUCT
Method B				
Diethylmesoxalate 2-carboxy-5-chlorophenylhydrazone	H_2SO_4	12	25	No reaction
Ethyl α,β-diketobutyrate α-2-carboxy-5-chlorophenylhydrazone	H_2SO_4	12	25	No reaction
Ethyl glyoxylate 2-carboxy-5-chlorophenylhydrazone	H_2SO_4	4	25	6-Chloroindazolone
	$(C_6H_5)_2O$	1.5	Reflux	Decomposition
	Tetralin	1.5	Reflux	No reaction
	p-Cymene	1.5	Reflux	No reaction
Ethyl glyoxylate 2-carboxy-4-chlorophenylhydrazone	H_2SO_4	4	25	5-Chloroindazolone
Method C				
Glyoxal phenylosazone	H_2SO_4	24	25	Phenylhydrazine
	HCl	6	Reflux	Phenylhydrazine
	$BF_3 \cdot (C_2H_5)_2O$	3.5	Reflux	Phenylhydrazine
	$ZnCl_2 + C_2H_5OH + HCl$	1	Reflux	Aniline
Method D				
α-Cyanoglyoxanilide 4-methoxy-2-nitrophenylhydrazone + P_2O_5	C_6H_6	7	Reflux	No reaction
α-Cyanoglyoxanilide imidochloride 4-methoxy-2-nitrophenylhydrazone + AlC_3	CS_2	2	25	No reaction
	$C_6H_5NO_2$	1.5	75	Decomposition

Anal. Calc'd for $C_{16}H_{13}N_5O_4$: C, 56.63; H, 3.86.
Found: C, 56.57; H, 4.12.

α-Cyanoglyoxanilide imidochloride 4-methoxy-2-nitrophenylhydrazone. Ten grams (0.029 mole) of the 4-methoxy-2-nitrophenylhydrazone of α-cyanoglyoxanilide and 9.3 g. (0.45 mole) of phosphorus pentachloride in 50 cc. of dry, thiophene-free benzene were refluxed for fifteen minutes, after which the evolution of hydrogen chloride ceased. The imidochloride separated from the cooled solution as orange needles and was removed by filtration and washed well with petroleum ether (b.p. 90–110°). Nine and one-half grams (0.027 mole, 90%) of crude product melting at 178–180° was obtained. Recrystallization from nitromethane raised the melting point to 185–186°.

Anal. Calc'd for $C_{16}H_{12}ClN_5O_3$: C, 53.71; H, 3.38; Cl, 9.91; N, 19.58.
Found: C, 53.77; H, 3.51; Cl, 10.07; N, 19.31.

The imidochloride was not hydrolyzed by hot 5 *N* sodium hydroxide, but it dissolved readily in 5 *N* ethanolic sodium hydroxide solution. Acidification of the solution yielded a compound, m.p. 218–220°, which did not depress the melting point of the anilide.

SUMMARY

Substituted phenylhydrazones which were regarded as possible intermediates in the formation of cinnolines have been prepared by the coupling of diazonium salts with compounds containing an active methylene group.

Four general methods of ring closure used in quinoline formation have been applied to cinnoline formation without success. Indazolones were formed in one method.

URBANA, ILL.

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

APPLICATIONS OF THE MEERWEIN REACTION. PART IV. THE SYNTHESIS OF NEW MONO- AND DI-SUBSTITUTED STILBENES

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The ability of unsaturated acids to undergo a Meerwein coupling with *meta*-substituted anilines (1, 2) was exploited for the synthesis of the new *meta*-nitrostilbene (Ia). This compound is of special interest because of the many reaction possibilities of an aromatic nitro group. Several conversion products of Ia are described in the Experimental Part. 1-(*m*-Nitrophenyl)-4-phenyl-1,3-butadiene (II) was prepared in an analogous manner. It condensed with maleic anhydride in the same way as did the *p*-nitro compound, to yield the adduct III.

Selective reduction of nitrostilbenes to aminostilbenes is usually carried out by Pfeiffer's method (3) (stannous chloride in acetic acid). During catalytic reduction of these nitro compounds with palladium or Raney nickel, no marked inflection in the hydrogenation curve was observed after absorption of three moles of hydrogen. If the reaction is interrupted at this point, only the completely reduced amino ethane can be isolated. It is thus apparent that in the nitrostilbenes the speed of reduction of the two reducible groups is similar, although stilbene and nitrobenzene react at very different rates under comparable experimental conditions.

TABLE I

MELTING POINTS OF *trans*-NITROSTILBENES AND THEIR DERIVATIVES, °C

	UNSUBST	*o*-SUBST	*m* SUBST	*p*-SUBST
Nitrostilbene	124	78[a]	112	157[b]
Nitrostilbene dibromide	237	156[c]	185	198[b]
Aminostilbene		106[a]	120	151[b]
Acetaminostilbene		144[a]	192	225[b]
Aminodiphenylethane		33[d]	51	48[e]
Acetaminodiphenylethane		117[d]	129	134[f]

[a] Sachs and Hilpert, *Ber.*, **39**, 899 (1906).

[b] See Ref. 4.

[c] Pfeiffer, *Ber.*, **48**, 1048 (1915).

[d] Ruggli and Staub, *Helv. Chim. Acta*, **20**, 37 (1937).

[e] v. Braun, Deutsch, and Koscielski, *Ber.*, **46**, 1511 (1913).

[f] This substance, p-$CH_3CONHC_6H_4CH_2CH_2C_6H_5$, crystallized from petroleum ether (130°) in long rods. *Anal.* Calc'd for $C_{16}H_{17}NO$: C, 80.3; H, 7.1. Found: C, 80.9; H, 6.6.

In Tables I and II the melting points of the isomeric *trans*-nitrostilbenes and *trans,trans*-nitrophenylphenylbutadienes and their derivatives are collected for comparison. It is seen that the large differences between the *m*- and *p*- series vanish almost completely if the unsaturated linkages disappear, either by hydrogenation, or bromination, or addition of maleic anhydride. The high melting points of the *p*-substituted derivatives are therefore ascribed to the strong mesomeric effect of the *p*-nitro group.

Ortho-substituted anilines usually give low yields of coupling products. This was again found to be the case with *o*-toluidine, which yielded 12% of *o*-methylstilbene (see Table III) and still more with α-naphthylamine, which produced only traces of 2-(α-naphthyl)-1-phenylethylene (IV). The melting point of our product, 148–149°, differs from that given by Balla (4), 72.5–73.5°, and therefore the two compounds are probably *cis-trans* isomers.[1] The Meerwein reaction between cinnamic acid and *o*-anisidine gave very impure samples of *o*-methoxystilbene (V), which could not be induced to crystallize. When we attempted to purify the substance *via* its dibromide (2), a tribromo derivative (VI) was obtained, which upon debromination yielded 5-bromo-2-methoxystilbene (VII). The latter structure was proved by comparison with the coupling product of cinnamic acid and diazotized 5-bromo-2-methoxyaniline.

TABLE II

MELTING POINTS OF *trans,trans*-1-(NITROPHENYL)-4-PHENYL-1,3-BUTADIENE, °C

	UNSUBST.	*o*-SUBST.	*m*-SUBST.	*p*-SUBST.
Nitrodiphenylbutadiene	152	97[a]	146	172[b]
Tetrabromide	255	193	206	245–246[b]
Adduct with maleic anhydride	207[c]	196	211	213[b]
Aminodiphenylbutadiene		132[a]		167[b]
Acetaminodiphenylbutadiene			203	260

[a] See Ref. 10.
[b] See Ref. 11.
[c] Diels and Alder, *Ber.*, **62**, 2081 (1929).

TABLE III

METHYLSTILBENES

	M.P., °C	YIELD %	DIBROMIDE M.P., °C	DIHYDRO DERIV B.P., °C
o-Methylstilbene	(b.p. 125/0.15 mm.)	12	159	95–98/0.05
m-Methylstilbene[a]	48	14		
p-Methylstilbene	120[b]	40	188[b]	98–99/0.05[c]

[a] See Ref. 12.
[b] Compare Klages and Tetzner, *Ber.*, **35**, 3967 (1902); Späth, *Monatsh.*, **35**, 469 (1914).
[c] Compare Mann, *Ber.*, **14**, 1645 (1881).

It was previously reported (2) that *o*-chloroaniline gave a 9% yield of *o*-chlorostilbene and 10% of 1-(*o*-chlorophenyl)-4-phenyl-1,3-butadiene. We have now carried out the analogous coupling with *p*-methoxycinnamic acid and obtained an 8% yield of 2-chloro-4′-methoxystilbene (VIII). 2,6-Dichloroaniline gave no

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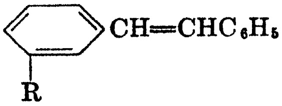
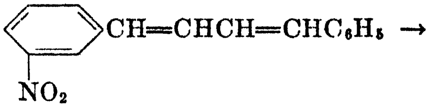
[1] β-Naphthylamine gave somewhat better yields. See Experimental Part.



I
a:R = NO_2
b:R = CH_3



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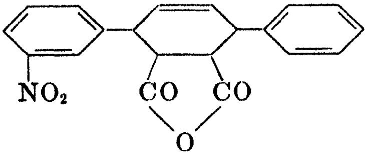

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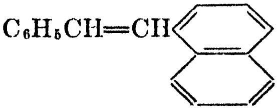

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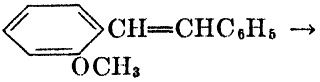

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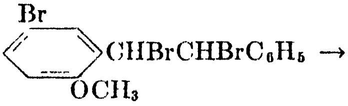

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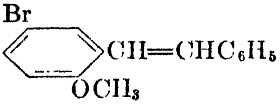

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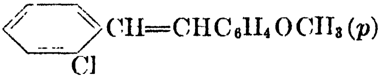

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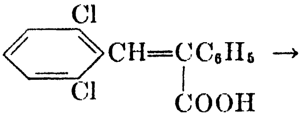

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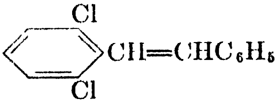

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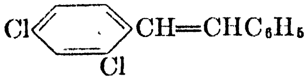

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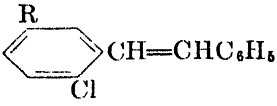
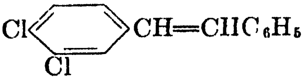


XII
a:R = Cl
b:R = CH_3



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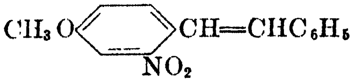

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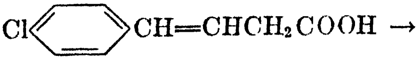

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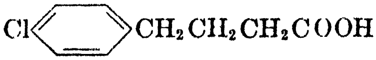

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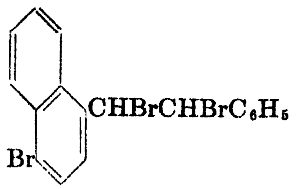
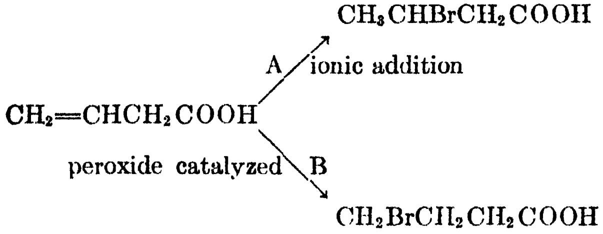


XVII



coupling product at all. The desired 2,6-dichlorostilbene (X) was, however, easily obtained by the classical method of Perkin from 2,6-dichlorobenzaldehyde and phenylacetic acid through decarboxylation of the intermediate carboxylic acid.

The Meerwein reaction of *ortho*-substituted anilines is markedly influenced by the presence of a second substituent. Thus 2,4-dichlorostilbene (XI) was obtained in 26% yield, 2,5-dichlorostilbene (XIIa) in 28%, and the 3,4-isomer (XIII) in 40% yield. 2-Chloro-5-methylaniline gave the corresponding stilbene (XIIb) in 27% yield. Comparison with *o*-chlorostilbene itself (9%) shows that the presence of an additional substituent diminishes the ortho-effect. 4-Methoxy-2-nitroaniline (5) was converted into 4-methoxy-2-nitrostilbene (XIV) in 18% yield.

The mechanism of the Meerwein reaction is still a controversial matter. Whereas Meerwein himself (6) proposed an ionic mechanism, consisting in the addition of the aryl cation to the α-carbon atom, *e.g.* of cinnamic acid, Koelsch (7) showed that acrylic and crotonic acids, which as catio-enoid systems add the anion of a hydrohalogen acid at the β-carbon atom, attach the aryl group at the same point. They thought it therefore probable that an aryl radical is the actual reacting form, and that the point of attack is determined by structural influences in the unsaturated acid. Thus, according to Koelsch, cinnamic acid adds the aryl radical at the α-carbon atom, because the odd electron on the β-carbon atom will be stabilized by resonance into the β-phenyl ring. Acrylic and crotonic acids, on the other hand, combine with their β-carbon atom, so that the odd electron on the α-carbon can resonate into the neighboring C=O group.

Now it must be borne in mind that all the β-unsaturated acids, which have been so far used for the Meerwein reaction, usually do not give different results when hydrohalogens are added to them, either as ions or by a radical mechanism (8). It appears therefore necessary to use an unsaturated acid, in which the disturbing catio-enoid system is absent, and therefore a clear distinction between the two reaction mechanisms can be made (9). When vinylacetic acid was coupled with diazotized *p*-chloroaniline, an acid was isolated in 5% yield, which represents one of the possible isomers of γ-(*p*-chlorophenyl)vinylacetic acid (XV). It was hydrogenated to γ-(*p*-chlorophenyl)butyric acid (XVI), identical with an authentic specimen (8). Kharasch and his co-workers have shown (9) that vinylacetic acid gives different results when hydrogen bromide is added by an ionic (scheme A) or radical mechanism (scheme B). Accordingly one would expect that the aryl cation would add at the β-carbon atom, and an aryl radical (which is less electrophilic than a halogen atom) to the γ-carbon atom. However, before final conclusions regarding the mechanism can be made, extension of these experiments to some more acids with terminal ethylenic groups appears necessary.

EXPERIMENTAL

m-Nitrostilbene (Ia) and derivatives. *m*-Nitroaniline (27 g.) was diazotized in hydrochloric acid solution and the clear diazo solution was added to cinnamic acid (30 g.) dissolved in acetone (150 cc.). The coupling reaction occurred at 14–16° during four hours. The solution was steam distilled, and the residue was extracted with benzene and washed with ammonia solution. Distillation gave a yellow oil, b.p. 170–175° (0.2 mm.), which crystallized on trituration with ethanol; yield 14.5 g., 33%. *m*-Nitrostilbene (Ia) crystallized from butanol in straw-yellow flat rods of m.p. 112°.

Anal. Calc'd for $C_{14}H_{11}NO_2$: C, 74.7; H, 4.9; N, 6.2.
Found: C, 74.7; H, 4.7; N, 6.0.

The *dibromide* was prepared in chloroform solution and crystallized from xylene-petroleum ether (130°) in branched leaflets of m.p. 184–185°.

Anal. Calc'd for $C_{14}H_{11}Br_2NO_2$: C, 43.6; H, 2.9; N, 3.6.
Found: C, 43.9; H, 2.6; N, 3.5.

m-Aminostilbene. *m*-Nitrostilbene (3 g.) was dissolved in acetic acid (50 cc.), containing 20 g. of stannous chloride, and saturated with dry hydrogen chloride (3). After a few minutes an exothermic reaction set in, and the complex salt crystallized out. It was filtered off and boiled with sodium hydroxide for two minutes. The supernatant oil solidified immediately. It was recrystallized first from ethanol, then from butyl acetate. *m*-Aminostilbene forms beautiful blocks of m.p. 119–120°.

Anal. Calc'd for $C_{14}H_{13}N$: C, 86.2; H, 6.7; N, 7.2.
Found: C, 86.0; H, 6.5; N, 7.5.

The acetyl derivative crystallized from acetic acid in tablets of m.p. 191–192°.

Anal. Calc'd for $C_{16}H_{15}NO$: C, 81.0; H, 6.3.
Found. C, 80.6; H, 6.3.

m-Aminodibenzyl. *m*-Nitrostilbene (3.5 g.) was dissolved in ethyl acetate (60 cc.) and reduced in the presence of Pd-$BaSO_4$. During 30 minutes about 1200 cc. of hydrogen was absorbed (calc'd: 1120 cc. for 760 mm. and 20°). The product distilled at 180° (6 mm.) as a thick yellow oil, which crystallized spontaneously. From petroleum ether (80°) thin, rhombic plates were obtained of m.p. 51°.

Anal. Calc'd for $C_{14}H_{15}N$: C, 85.3; H, 7.6; N, 7.1.
Found: C, 84.9; H, 7.7; N, 7.0.

3-Acetaminodibenzyl crystallized from a benzene-petroleum ether (80°) mixture in quadrangular plates of m.p. 128–129°.

Anal. Calc'd for $C_{16}H_{17}NO$: C, 80.3; H, 7.1; N, 5.9.
Found: C, 80.6; H, 7.0; N, 6.0.

1-(m-Nitrophenyl)-4-phenyl-1,3-butadiene (II) and derivatives. The Meerwein reaction between diazotized *m*-nitroaniline (18 g.) and 1-carboxy-4-phenyl-1,3-butadiene (22 g.)

proceeded at 24–30° during four hours. The mixture was worked up as above and yielded, after steam distillation, a crude product which crystallized directly upon treatment with hot acetic acid. II was recrystallized first from butanol, then from acetic acid, m.p. 146°, yield 4 g., 12%.

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6.
Found: C, 76.1; H, 5.5; N, 5.8.

The tetrabromide, which was prepared in chloroform solution, had the m.p. 206° after recrystallization from xylene-petroleum ether (130°).

Anal. Calc'd for $C_{16}H_{13}Br_4NO_2$: C, 33.6; H, 2.3.
Found: 33.8; H, 2.3.

When the tetrabromide was treated with potassium iodide in acetone solution, the original butadiene was recovered.

1-(*m*-Nitrophenyl)-4-phenyl-1,3-butadiene (1 g.) was heated on a water-bath with maleic anhydride (2 g.) for four hours and the mixture was thereafter dissolved in hot acetic acid. On cooling, the adduct (III) was deposited, which crystallized from acetic anhydride in tablets of m.p. 211°; yield quantitative.

Anal. Calc'd for $C_{20}H_{16}NO_5$: C, 68.8; H, 4.3.
Found: C, 68.9; H, 4.2.

1-(*m*-Aminophenyl)-4-phenyl-1,3-butadiene was obtained in a manner analogous to the preparation of *m*-aminostilbene. As it was difficult to purify it from the last traces of stannic oxides, it was acetylated directly. 1-(*m*-Acetaminophenyl)-4-phenyl-1,3-butadiene crystallized from xylene in rods of m.p. 203°.

Anal. Calc'd for $C_{18}H_{17}NO$: C, 82.1; H, 6.5.
Found: C, 81.8; H, 6.0.

1-(*o*-Nitrophenyl)-4-phenyl-1,3-butadiene was prepared according to Bachman and Hoaglin (10) by the appropriate Meerwein reaction of *o*-nitroaniline.

Its tetrabromide was recrystallized from petroleum ether (130°) and had m.p. 193°.

Anal. Calc'd for $C_{16}H_{13}Br_4NO_2$: C, 33.6; H, 2.3.
Found: C, 33.4; H, 2.3.

The adduct with maleic anhydride was prepared as above. It crystallized from butyl acetate in rods, m.p. 196°.

Anal. Calc'd for $C_{20}H_{16}NO_5$: C, 68.8; H, 4.3,
Found: C, 69.0; H, 4.5.

The following new derivatives of 1-(*p*-nitrophenyl)-4-phenyl-1,3-butadiene (11) were prepared:

1-(*p*-Acetaminophenyl)-4-phenyl-1,3-butadiene crystallized from butyl acetate in yellowish short rods of m.p. 260°.

Anal. Calc'd for $C_{18}H_{17}NO$: C, 82.1; H, 6.5.
Found: C, 82.0; H, 6.5.

1-(*p*-Aminophenyl)-4-phenyl-1,3-butadiene reacted with diphenylketene in benzene solution. 1-(*p*-Diphenylacetaminophenyl)-4-phenyl-1,3-butadiene crystallized from ethyl benzoate in short rods of m.p. 240–241°.

Anal. Calc'd for $C_{30}H_{25}NO$: C, 86.75; H, 6.0; N, 3.4.
Found: C, 86.8; H, 6.4; N, 3.6.

Catalytic reduction produced 1-(*p*-aminophenyl)-4-phenylbutane of m.p. 32°, b.p. 178° (0.1 mm.).

Anal. Calc'd for $C_{16}H_{19}N$: C, 85.3; H, 8.4.
Found: C, 85.0; H, 8.2.

Its acetyl derivative crystallized from ethanol in glistening plates of m.p. 135°.

Anal. Calc'd for $C_{18}H_{21}NO$: C, 80.9; H, 7.9; N, 5.2.
Found. C, 80.6; H, 8.0; N, 5.6.

Methylstilbenes (see Table III). *o*-Methylstilbene was obtained by the appropriate Meerwein reaction in 12% yield; colorless oil of b.p. 120–125° (0.15 mm.).

Anal. Calc'd for $C_{15}H_{14}$: C, 92.8; H, 7.2.
Found: C, 92.4; H, 7.6.

Its dibromide crystallized from isopropanol and showed the m.p. 158–159°.

Anal. Calc'd for $C_{15}H_{14}Br_2$: C, 50.8; H, 4.0.

Found: C, 50.6; H, 4.4.

Catalytic reduction yielded *o*-methyldibenzyl as a colorless oil of b.p. 95–98° (0.05 mm.)

Anal. Calc'd for $C_{15}H_{16}$: C, 91.8; H, 8.2.

Found: C, 91.8; H, 8.2.

m-Methylstilbene (I b) (12) was obtained as an oil of b.p. 135–140° (0.1 mm.,) which crystallized slowly. After two recrystallizations from methanol it was obtained as yellowish leaflets of m.p. 48°; yield 14%.

Anal. Calc'd for $C_{15}H_{14}$: C, 92.8; H, 7.2.

Found: C, 93.1; H, 7.4.

The dibromide of (I b) crystallized from petroleum ether (130°) is prismatic plates of m.p. 174–176°.

Anal. Calc'd for $C_{15}H_{14}Br_2$: C, 50.8; H, 4.0.

Found: C, 50.6; H, 4.1.

Coupling with α-naphthylamine. The Meerwein reaction between diazotized α-naphthylamine and cinnamic acid was accomplished at 22–26°. The black tar which remained after steam distillation, was distilled *in vacuo* and yielded a very small fraction of b.p. 170° (14 mm.), which crystallized from petroleum ether (130°) in flakes of m.p. 148–149°.

Anal. Calc'd for $C_{18}H_{14}$: C, 93.9; H, 6.1.

Found: C, 93.6; H, 5.9.

With bromine in chloroform simultaneous addition at the ethylenic double bond and substitution in the ring took place, to yield a tribromo derivative of the possible structure XVII. The substance crystallized from petroleum ether (130°) in colorless leaflets of m.p. 165°.

Anal. Calc'd for $C_{18}H_{14}Br_2$: C, 55.4; H, 3.6.

for $C_{18}H_{13}Br_3$: C, 46.1; H, 2.8.

Found: C, 45.9; H, 2.6.

Coupling with β-naphthylamine. The reaction between diazotized β-naphthylamine and cinnamic acid proceeded at 5–15°. The tar, which remained after steam distillation, crystallized upon trituration with methanol. Recrystallization from petroleum ether (130°) gave 2-(β-naphthyl)-1-phenylethylene as white leaflets of m.p. 143°; yield 5%.

Anal. Calc'd for $C_{18}H_{14}$: C, 93.9; H, 6.1.

Found: C, 94.0; H, 6.4.

The dibromide was prepared in chloroform solution. It crystallized from petroleum ether (130°) in prisms of m.p. 186–187°.

Anal. Calc'd for $C_{18}H_{14}Br_2$: C, 55.4; H, 3.6.

Found: C, 55.3; H, 3.7.

Coupling with o-anisidine. The crude *o*-methoxystilbene (13) was obtained as a reddish oil of b p. 138–140° (0.15 mm.). For purification, it was brominated in chloroform solution. The product crystallized from a mixture of xylene and petroleum ether (130°) in beautiful prisms of m.p. 190–192° (VI).

Anal. Calc'd for $C_{15}H_{14}Br_2O$: 48.6; H, 3 8; OCH_3, 8.4.

for $C_{15}H_{13}Br_3O$: C, 40.1; H, 2.9; OCH_3, 6.9.

Found: C, 39.9; H, 3.0; OCH_3, 6.8.

Dehalogenation of VI with potassium iodide in acetone gave an oil which crystallized after one weeks standing. The product (VII) crystallized from ethanol in colorless needles of m.p. 74°.

Anal. Calc'd for $C_{15}H_{13}BrO$: C, 62.3; H, 4.5.

Found: C, 62.1; H, 4.5.

Synthesis of 5-bromo-2-methoxystilbene (VII). 5-Bromo-2-methoxyaniline was prepared according to Kohn and Karlin (15). Its diazo derivative coupled with cinnamic acid under the usual conditions at 20–25°. The crude product was purified by distillation, b.p. 225–230°

(1.25 mm.), the distillate solidified spontaneously. It and its dibromide did not depress the melting points of the substances VI and VII described above.

2-Chloro-4′-methoxystilbene (VIII). The coupling between diazotized *o*-chloroaniline and *p*-methoxycinnamic acid proceeded at 17–20°. The crude product was distilled *in vacuo*, b.p. 180–185° (0.05 mm.). The oil so obtained solidified upon treatment with methanol. The substance (VIII) crystallized from the same solvent in prisms of m.p. 64°;[2] yield 14%.

Anal. Calc'd for $C_{15}H_{13}ClO$. C, 73.8; H, 5.3.
Found: C, 73.4; H, 5.3.

The dibromide crystallized from petroleum ether (130°) in clusters of leaflets, m.p. 148°.

Anal. Calc'd for $C_{15}H_{13}Br_2ClO$: C, 44.6; H, 3.2.
Found: C, 44.9; H, 3.5.

The stilbene VIII could not be demethylated by boiling 48% hydrobromic acid.

Dichlorostilbenes (see Table IV). 2,4-, 2,5-, and 3,4-Dichlorostilbene were prepared by the appropriate Meerwein reactions. The coupling of diazotized 2,6-dichloroaniline with cinnamic acid was unsuccessful. The compound X was therefore synthesized by Perkin's method.

2,6-Dichlorostilbene (X). 2,6-Dichlorobenzaldehyde (26 g.) and dry sodium phenylacetate (26 g.) were heated in boiling acetic anhydride (60 cc.) for eight hours. Then acetic acid (200 cc.) was added and the solution filtered. The filtrate, on standing overnight, deposited 25 g. (57%) of crystals (IX). This product crystallized from acetic acid in prismatic columns of m.p. 235°.

Anal. Calc'd for $C_{15}H_{10}Cl_2O_2$: C, 61.4; H, 3.4.
Found: C, 61.2; H, 3.8.

Decarboxylation. The acid (IX) (20 g.) was dissolved in quinoline (200 cc.) and basic copper carbonate (20 g.) added. Reaction started at 140° and was over after about half an hour. The solution was then boiled for ten minutes and steam-distilled. The non-volatile residue crystallized from propanol in prismatic plates of m.p. 89–90° (X), yield 10 g., or 60%.

Anal. Calc'd for $C_{14}H_{10}Cl_2$: C, 67.7; H, 4.0.
Found: C, 67.6; H, 4.4.

The dibromide of X crystallized from petroleum ether (130°) in prismatic plates of m.p. 136°.

Anal. Calc'd for $C_{14}H_{10}Br_2Cl_2$: C, 41.2; H, 2.5.
Found: C, 40.9; H, 2.2.

Bromination of the acid IX, on the other hand, was unsuccessful.

Coupling with vinylacetic acid. *p*-Chloroaniline (12 g.) was diazotized in the usual way, and the diazo solution added to vinylacetic acid (8.6 g.) in ice-cold acetone (200 cc.). The coupling reaction proceeded at 15°. After steam distillation, the non-volatile syrup was dissolved in benzene and the organic acids extracted from it by sodium hydroxide solution. This solution was boiled with charcoal, filtered, and stirred into ice-cold hydrochloric acid. A small precipitate was obtained which crystallized from petroleum ether (80°) in twinned plates of m.p. 107° (XV), yield 1 g., 5%.

Anal. Calc'd for $C_{10}H_9ClO_2$: C, 61.2; H, 4.6.
Found: C, 61.5; H, 4.4.

The unsaturated acid (XV) (0.8 g.) in acetic acid (20 cc.) was reduced over palladium-barium sulfate at 23° (758 mm.). The required amount of hydrogen was absorbed during 15 minutes. Distillation at 140–150° (1 mm.) gave an oil which solidified spontaneously (XVI), m.p. 55° [Lit. (16) 62°].

For easier identification, the chloride of XVI was prepared with thionyl chloride in boil-

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[2] Thus all the three isomeric chloro-4′-methoxystilbenes are now known: 3-Chloro-4′-methoxystilbene m.p. 96° [Jenkins and Richardson *J. Am. Chem. Soc.* **55**, 3874 (1933)]; 4-chloro-4′-methoxystilbene, m.p. 184° [v. Walter and Wetzlich *J. prakt. Chem.* (2) **67**, 175 (1900)].

TABLE IV

Unilateral Disubstituted Stilbenes and their Derivatives

Stilbenes, Ar—CH=CH—C_6H_5

Ar =	Yield %	M.P., °C	Solvent	Crystal Form	Formula	Analyses Calc'd C	Analyses Calc'd H	Analyses Found C	Analyses Found H
2,4-Dichlorophenyl[a]	26	79–80	Pet. ether 80°	Leaflets	$C_{14}H_{10}Cl_2$	67.7	4.0	67.6	3.8
2,5-Dichlorophenyl[b]	28	62	Methanol	Needles	$C_{14}C_{10}Cl_2$	67.7	4.0	67.6	4.0
3,4-Dichlorophenyl	40	86–87	Ethanol	Leaflets	$C_{14}H_{10}Cl_2$	67.7	4.0	67.6	3.8
2,6-Dichlorophenyl[c]	60	89–90	Propanol	Prismatic plates	$C_{14}H_{10}Cl_2$	67.7	4.0	67.6	4.4
2-Chloro-5-methylphenyl	27	b.p. 150/3 mm.			$C_{15}H_{13}Cl$	78.9	5.7	79.1	5.7
4-Methoxy-2-nitrophenyl	18	116	Acetic acid	Prismatic blocks	$C_{15}H_{13}NO_3$	70.6	5.1	71.2	5.5
5-Bromo-2-methoxyphenyl	28	74	Ethanol	Needles	$C_{15}H_{13}BrO$	62.3	4.5	62.1	4.5

Dibromides, Ar—CHBr—CHBr—C_6H_5

Ar =	Yield %	M.P., °C	Solvent	Crystal Form	Formula	Analyses Calc'd C	Analyses Calc'd H	Analyses Found C	Analyses Found H
2,4-Dichlorophenyl		146	Pet. ether 80°	Prismatic plates	$C_{14}H_{10}Br_2Cl_2$	41.2	2.5	41.3	2.9
2,5-Dichlorophenyl		188	Xylene	Prismatic blocks	$C_{14}H_{10}Br_2Cl_2$	41.2	2.5	41.7	2.2
3,4-Dichlorophenyl		182	Xylene	Prismatic rods	$C_{14}H_{10}Br_2Cl_2$	41.2	2.5	41.6	2.3
2,6-Dichlorophenyl		136	Pet. ether 130°	Prismatic plates .	$C_{14}H_{10}Br_2Cl_2$	41.2	2.5	40.9	2.2
2-Chloro-5-methylphenyl		158	Pet. ether 130°	Prismatic rods	$C_{15}H_{13}Br_2Cl$	46.4	3.3	46.2	3.1

Dihydro Derivatives, Ar—$CH_2CH_2C_6H_5$

Ar =	Yield %	M.P., °C	Solvent	Crystal Form	Formula	Analyses Calc'd C	Analyses Calc'd H	Analyses Found C	Analyses Found H
2,4-Dichlorophenyl		b.p. 128–130/0.1 mm.			$C_{14}H_{12}Cl_2$	67.2	4.8	67.3	4.7
2,5-Dichlorophenyl		b.p. 133/0.06 mm.			$C_{14}H_{12}Cl_2$	67.2	4.8	67.4	4.8
3,4-Dichlorophenyl		53 b.p. 173/0.6 mm.			$C_{14}H_{12}Cl_2$	67.2	4.8	67.5	4.7

[a] Meerwein (6), who first prepared this stilbene, reports m.p. 77.5°

[b] This stilbene could be obtained pure only by decomposition of its dibromide with sodium iodide.

[c] This dichlorostilbene was prepared by Perkin's method (see Experimental Part).

ing benzene and converted directly into the anilide. The latter was recrystallized from petroleum ether (60°), forming elongated, sharp needles of m.p. 102°.

Anal. Calc'd for $C_{16}H_{16}ClNO$: C, 70.3; H, 5.9.

Found: C, 70.0; H, 5.7.

Both the acid (XVI) and its anilide did not depress the m.p. of γ-(*p*-chlorophenyl)butyric acid and its anilide, prepared according to Skraup and Schwamberger (16).

Acknowledgment. We wish to thank Mr. A. Loeffler for his technical assistance in the experiments described here.

SUMMARY

1. The Meerwein reaction between diazotized anilines and cinnamic acids has been applied to vairious meta-, ortho-, and di-substituted anilines. The coupling with α-naphthylamine gave a 2-(α-naphthyl)-1-phenylethylene, isomeric with the compound of the same structure described by Balla (4). 2,6-Dichlorostilbene could not be prepared in this way, but was obtained by the Perkin condensation of 2,6-dichlorobenzaldehyde with phenylacetic acid.

Selective catalytic reduction of the nitrostilbenes in the nitro group only could not be achieved.

2. The Meerwein reaction between diazotized *p*-chloroaniline and vinylacetic acid gave γ-(*p*-chlorophenyl)vinylacetic acid. If the reaction is regarded as ionic, the point of attachment of the diazo cation at the γ-carbon atom corresponds to the point of addition of the proton in the reaction with hydrobromic acid. If, however, comparison is made with the peroxide-catalyzed addition reaction, one should expect attachment of the aromatic radical at the β-carbon atom. Our result, therefore, points to an ionic mechanism, at least in the case of vinylacetic acid.

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[Contribution from the Sterling Chemistry Laboratory and the Bingham Oceanographic Laboratory, Yale University]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XX. REMARKS CONCERNING THE STRUCTURE OF STEROLS FROM MARINE INVERTEBRATES

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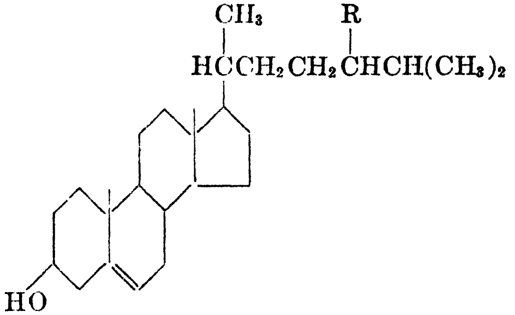
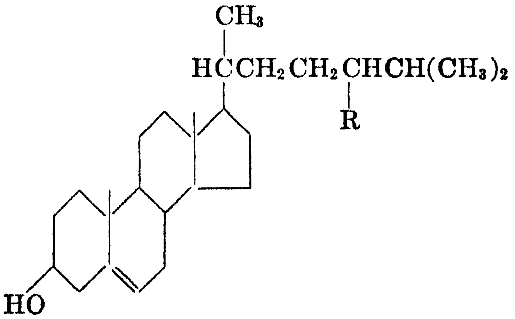
In 1941, Fernholz and Ruigh (1) convincingly demonstrated that campesterol and campestanol differ from 22,23-dihydrobrassicasterol and ergostanol solely in the optical configuration at C-24. Since then it has been shown that this C-24 epimerism is not infrequently encountered among naturally occurring sterols, and that the C_{28}-sterols from marine invertebrates such as the stellasterols and stellastenols (2), neospongosterol (3) and chalinasterol (4) predominantly belong to the campestanol series. In conformity with the customary designation of steroid epimers, it is here proposed to refer to the ergostanol and campestanol series as the 24-(α)- and 24-(β)-methylcholestanol series, and following a suggestion by Ruigh (5), to write the 24-methyl group above the side chain in the α-series (I) and below the side chain in the β-series (II).



I. C-24-α-Sterol

22,23-Dihydrobrassicasterol, R = CH_3



II. C-24-β-Sterol

Campesterol, R = CH_3

Sufficient data have now become available for the rotations of various representatives of both series to permit an evaluation of the contributions of the 24-α- and 24-β-methyl groups to the molecular rotations.[1] As has been shown by Callow and Young (6), Wallis and co-workers (7), and recently also by Barton (8), examination of differences in molecular rotations of steroids frequently provides a useful tool in establishing the structure of a steroid or its uniformity.

TABLE I

MOLECULAR ROTATIONS OF THE CHOLESTANOL AND 24-METHYLCHOLESTANOL SERIES

COMPOUND	$[M]_D$[a]			Δ_1	Δ_2
	Cholestanol	24-α-Methyl	24-β-Methyl		
Stanol	+93	+64	+125	−29	+32
Stanylacetate	+60	+27	+80	−33	+20
5,6-Stenol	−151	−184	−132	−33	+19
5,6-Stenylacetate	−184	−203	−159	−19	+25
5,6-Stenylbenzoate	−64	−96	−50	−32	+14
Average				−29	+22

[a] Molecular rotations according to Barton (8).

TABLE II

MOLECULAR ROTATIONS OF THE 8,14- AND 14,15-STENOLS

COMPOUND	$[M]_D$[a]			Δ_1	Δ_2
	Cholestanol	24-α-Methyl	24-β-Methyl		
8,14-Senol	+81	+48	+80	−33	−1
8,14-Stenylacetate	+43	+4	+57	−39	+14
8,14-Stenylbenzoate	+39	+5		−34	
14,15-Stenol	+124	+72	+116	−52	−12
14,15-Stenylacetate	+94	+31	+84	−63	−10
14,15-Stenylbenzoate	+157	+101		−56	

[a] Molecular rotations according to Barton (8).

In Table I the molecular rotations of cholestanol and its derivatives are compared with those of 24-α- and 24-β-methyl cholestanol and their corresponding derivatives. The figures Δ_1 and Δ_2 represent the differences in molecular rotations between the series cholestanol: 24-α-methylcholestanol (ergostanol) and cholestanol: 24-β-methylcholestanol (campestanol). It may be seen that the presence of a 24-α-methyl group increases the levo-rotation by a comparatively uniform value, the average $\Delta_1 = -29$. In the absence of "vicinal action" it is to be expected that a 24-β-methyl group increases the dextro-rotation and that the average $\Delta_2 = +29$. The observed average value for $\Delta_2 = +22$ agrees quite well with this expectation, particularly since the permissible error in molecular rotations is ± 10. At present the data for the α-series appear to be more accurate than those for the β-series. In the latter, considerable difficulties are frequently encountered in obtaining products free from the more levo-rotatory α-epimers.

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[1] Molecular Rotation, $[M]_D = \frac{[\alpha]_D \times \text{Mol. weight}}{100}$

Table II contains a comparison of the molecular rotations of the corresponding 8, 14- and 14, 15-stenols (8). The average $\Delta_1 = -35$ for the 8, 14-stenols agrees fairly well with the corresponding value in Table I. The Δ_2-values, however, which are based on the rotations reported for "α"-stellastenol (2) are unsatisfactory. They suggest either that "α"-stellastenol does not possess the structure of a 24-methylcholesten-8, 14-ol, or that it contains significant quantities of the more levo-rotatory 24-α-methyl epimer. On the basis of other evidence (4), the latter possibility appears to be more probable. The calculated values for the specific rotations of 24-β-methylcholesten-8, 14-ol and its acetate are +26.5° and +17.5°, and those reported for "α"-stellastenol and its acetate are +20° and +13°. The average Δ_1 for the 14, 15-stenols is -55. This difference of 20–25 over the other Δ_1 values is greater than can be accounted for by permissible experimental error and therefore suggests the influence of "vicinal action".

Dirscherl and Nahm (9) have presented evidence pointing to the occurrence of C-24 epimerism among the "sitosterols" or derivatives of 24-ethylcholestanol. They found that the oxidation of β- and γ-sitosterylacetate afforded the dextro- and levo-rotatory 6-methyl-5-ethylheptanone-2 respectively. These observations suggest that β- and γ-sitosterol differ from each other only in the configuration at C-24. As yet, however, only β-sitosterol (22, 23-dihydrostigmasterol) has convincingly been shown to be a 24-ethylcholesterol. In the case of γ-sitosterol only the structure of the side chain has been established, but a proof of the identity of the remainder of the molecule, including the configuration at C-20, with that of cholesterol is still missing. The possibility is not excluded, for example, that in γ-sitosterol the configuration at C-20 is the opposite of that of cholesterol. From the data reported by Plattner and Pataki (10) for the specific rotation of the C-20-epimeric nor-allocholanic acids it may be deduced that epimerism at C-20 does not exert a profound influence upon the optical rotation. As shown in Table III, the average difference of 14 between the molecular rotations of representatives of the normal and iso-series is close to the limits of experimental error.

In Table IV the differences between the molecular rotations of members of the cholestanol and stigmastanol series, Δ_1, are compared with those of the cholestanol and γ-sitostanol series, Δ_2. As is to be expected, the average contribution of the C-24-ethyl group, $\Delta_1 = +6$, is less than that of the methyl group. If the γ-sitostanol series is epimeric at C-24 with the stigmastanol series, the molecular rotations of its members should differ by an average of -6 from those of the corresponding members of the cholestanol series. This expectation holds true within the limits of experimental error among the saturated compounds, where the average $\Delta_2 = -5$. In the 5, 6-unsaturated series, however, the average $\Delta_2 = -31$ is considerably greater than can be accounted for by experimental error. This discrepancy suggests either that γ-sitosterol is not a C-24-epimer of 22,23-dihydrostigmasterol, or more likely that the samples which have so far been described contain a more levo-rotatory component, such as for example 22,23-dehydro-γ-sitosterol.

TABLE III

MOLECULAR ROTATIONS OF EPERIMERIC NOR-ALLOCHOLANIC ACIDS

DERIVATIVE	CONFIGURATION AT C-20		
	Normal	Iso	Difference
3-β-Hydroxy	+84	+67	−17
3-β-Hydroxy methyl ester	+71	+63	−12
3-β-Acetoxy methyl ester	+49	+34	−15
3-β-Hydroxy-5,6-enic acid	−153	−165	−12
Average			−14

TABLE IV

MOLECULAR ROTATIONS OF THE CHOLESTANOL AND 24-ETHYLCHOLESTANOL SERIES

DERIVATIVE	$[M]_D$						
	Cholestanol[a]	Stigmastanol[a]		γ-Sitostanol[a]		Poriferastanol[b]	
			Δ_1		Δ_2		Δ_2
Stanol	+93	+100	+7	+83	−10	+90	−3
Stanylacetate	+60	+69	+9	+46	−14	+70	+10
Stanylbenzoate	+98	+104	+6	+104	+6	—	—
Stanone	+158	+170	+12	+157	−1	+171	+13
5,6-Stenol	−151	−149	+2	−178	−27	−153	−2
5,6-Stenylacetate	−184	−178	+6	−210	−26	−189	−5
5,6-Stenylbenzoate	−64	−73	−9	−104	−40	−83	−19
5,6-Stenyl-*m*-dinitrobenzoate	−81	−61	+20	—	—	−85	−4
4,5 Stenone	+357	+354	−3			+330	−27
Average			+6		−16		−5

[a] Data according to Barton (8).

[b] Average data from various samples of different origin.

In previous communications (11, 12) it had been shown that certain sponges contain a mixture of poriferasterol and its 22,23-dihydro derivative, clionasterol. The conversion of the former into the latter has now been accomplished by means of the customary selective hydrogenation by way of the i-ether. It had been demonstrated that poriferasterol is an isomer of stigmasterol and it differs from the latter only in the arrangement of the terminal seven carbon atoms of the side chain. Ozonolysis of poriferasterol had been reported to afford an aldehyde, $C_7H_{14}O$, which was isolated in the form of its 2,4-dinitrophenylhydrazone, m.p. 113–114°, $[\alpha]_D$ ±0°. The ozonolysis has now been repeated with samples of poriferasterol obtained from several different species of sponges. In all instances aldehydes were obtained, the 2,4-dinitrophenylhydrazones of which melted at 116–118° and were dextro-rotatory, $[\alpha]_D + 4°$. The corresponding derivative of ethylisopropylacetaldehyde, obtained from stigmasterol under analogous conditions, melted at 120° and was levo-rotatory, $[\alpha]_D -3$. The melting point of the derivative of the synthetic *dl*-aldehyde is 115–117°, as reported by Dirscherl (13). These observations suggest the probability that stigmasterol and poriferasterol, and therefore also β-sitosterol and clionasterol are C-24 epimers. This probability is strengthened by a comparison of the differences in molecular rotations, Δ_3, between derivatives of the cholestanol and poriferastanol series, which are included in Table IV. Assuming poriferastanol to be the C-24 epimer of stigmastanol, and clionasterol to be the C-24 epimer of 22,23-dehydrostigmasterol (β-sitosterol), the observed average $\Delta_3 = -5$ agrees well with the expected value, and better than the average $\Delta_2 = -16$. On the basis of the values given in Table IV one should therefore assume that both γ-sitostanol and poriferastanol are C-24 epimers of stigmastanol and that they are consequently identical substances. A comparison of the physical properties of the respective compounds, shown in Table V, suggests that this is probably the case. The lack of agreement between the data for the unsaturated compounds, γ-sitosterol and clionasterol, may be due, as pointed out above, to the presence in the former of higher-melting, and more levo-rotatory impurities.

In connection with the discussion of the C-24-methylcholestanols it had been proposed above to refer to the different series by the prefix α or β. Similar designations may also be assigned to the C-24-ethylcholestanol series once their configuration at C-24 has been related to one or the other of the C-24-methyl series. The fact that upon oxidation campesterol affords the dextro-5,6-dimethylheptanone-2 (1), and β-sitosterol the dextro-5-methyl-6-ethylheptanone-2 (9) does not imply that the two sterols have similar configurations at C-24 (5). On the contrary, one should expect on the basis of the rules formulated by Marker (14) that the levo-rotatory dimethylheptanone and the dextro-rotatory methylethylheptanone have identical configurations, and that therefore ergostanol and stigmastanol belong to the same α-series. Similar conclusion can be drawn from a comparison of the differences in molecular rotations between the semicarbazones and the 2,4-dinitrophenylhydrazones of the aldehydes obtained from stigmasterol and ergosterol, which are shown in Table VI. In both cases these differences are of the same direction and magnitude.

Another sterol, ostreasterol, believed to be isomeric with stigmasterol, was isolated in 1934 by one of the present authors (15) from the oyster, *Ostrea virginica*, and other bivalves. About the same time Tsujimoto and Koyanagi (16) reported the isolation of a similar substance, conchasterol, from a variety of mollusks, and of shakosterol, a sterol characterized by the high melting point of its acetate. A survey of the various sterols which have so far been isolated from mollusks is given in Table VII. Since then the structure of a number of "phytosterol-like" sterols, *i.e.* sterols of the order C_{28} and C_{29}, has been established, and the nature of the mollusks sterols may now be re-examined under the light of the new evidence. As shown in Table VIII, the data for ostreasterol show such great similarity to those of chalinasterol, $C_{28}H_{46}O$, as to suggest the identity of the two sterols. In addition, the bromine content (41.93%) reported for ostreasterylacetate tetrabromide agrees more closely with the calculated value for a C_{28}- (42.04%) than for a C_{29}-sterylacetate tetrabromide (41.30%). The original assumption that ostreasterol is an isomer of stigmasterol was based primarily on the conversion of ostreasterol to a stanol, similar in properties to "sitostanol". Since the hydrogenation had not been carried out with a highly purified sample, this evidence must now be regarded as of doubtful value.

TABLE V

COMPARISON OF DERIVATIVES OF γ-SITOSTANOL AND PORIFERASTANOL

DERIVATIVE	γ-SITOSTANOL[a]		PORIFERASTANOL[b]	
	M.p., °C	α_D°	M.p., °C	α_D°
Stanol...	143–145	+18 to +21	143	+21
Stanylacetate	142–145	+9 to +12.5	142	+15
Stanone	163	+38	161	+41
5,6-Stenol	143–148	−41 to −45	139	−37
5,6-Stenylacetate	143	−45 to −48	137	−41.5
5,6-Stenylbenzoate	152	−20	141	−16

[a] Data according to references 25 to 29.

[b] Average data from various samples of different origin.

TABLE VI

COMPARISON OF MOLECULAR ROTATIONS OF ALDEHYDES FROM ERGOSTEROL AND STIGMASTEROL

Derivative	$[M]_D$ OF $RCH(CHO)CH(CH_3)_2$[a]	
	$R = CH_3$	$R = C_2H_5$
Semicarbazone	−82	+16
2,4-Dinitrophenylhydrazone	−106	−9
Difference	−24	−25

[a] All rotations were taken in chloroform.

It has been found in recent years in this laboratory that the composition of the sterol mixture in the oyster undergoes seasonal variations, and considerable difficulties have been encountered in obtaining sizeable quantities of ostreasterol purified over its acetate tetrabromide of m.p. 150°. In many instances mixtures of tetrabromides were obtained which melted between 150–210°, and which proved difficult to separate. In a previous communication (19) the isolation of a small amount of an acetate tetrabromide of m.p. 200° has been described and the suggestion made that it is identical with the tetrabromide of stigmasterylacetate. In view of more recent findings this identification must now be regarded as inadequate. It appears at present most likely that the compound

TABLE VII

STEROLS FROM MOLLUSKS

	PER CENT FAT OF WET WEIGHT	PER CENT UNSAPONIFIABLE	STEROL M.P., °C.	ACETATE, M.P., °C.	REF.
Pelecypoda (Bivalves)					
Tapes phillippinarium	0.8	15.3	135–136	137	16a
Corbicula leana	0.7	14.8	135–136	126–127	16a
Cristaria plicata	1.3	13	133–134	137–138	16a
Meretric meretrix	0.7	12.6	133–134	137–138	16b
Ostrea gigas	1.4	11.8	136–137	135–136	16b
Ostrea virginica	1.5	11	142–143	134–135 (ostreasterol)	15
Mya arenaria	1.6	—	138–139	127–128	16b
Velsella modiolus	3(?)	12	135–136	127–128	16b
Tridacna gigas	0.9	11.5	146–147	156–157 (shakosterol)	16c
Venus mercenaria	0.7	15	139–140	131	15
Modiola modiola	1.0	16		131	15
Average	1.0	13.3			
Gastropoda (Snails)					
Haliotis gigantea	1.0	10		cholesterol	16a
Turbo cornutus	1.0	14.6		cholesterol	16a
Rapana thomasiana	1.8	15	140	120 cholesterol	16b
Cellana nigrolineata	4.2	15		cholesterol	16b
Tegula xanthostigma	2.8	11		cholesterol	16c
Fulgur sp.	1.5	12.3		cholesterol	15
Buccinum undataum				cholesterol	17, 18
Arion empiricorum				cholesterol	17
Helix pomatia				cholesterol	17, 22
Average	2 0	13.0			
Cephalopoda					
Sepia officinalis				cholesterol	23, 24

TABLE VIII

COMPARISON OF OSTREASTEROL AND CHALINASTEROL

DERIVATIVE	OSTREASTEROL (15)		CHALINASTEROL (4)	
	M.p., °C.	$[\alpha]_D^{\circ}$	M.p., °C.	$[\alpha]_D^{\circ}$
Sterol	143	−43.6	144	−42
Sterylacetate	134.5	−46	136	−46
Sterylbenzoate	147		147–149	
Sterylacetate tetrabromide	150–151		150–155	

was impure brassicasterylacetate tetrabromide. The acetate tetrabromide of m.p. 176° which Fantl (20) obtained from the sterols of *Mytilus* was probably a mixture of ostrea(chalina-)sterylacetate tetrabromide and the higher-melting bromide. The presence of cholesterol in bivalves was first demonstrated by Fantl, who isolated this sterol from *Mytilus*. More recently cholesterol has also been shown in this laboratory to occur in small amounts in the mixture of oyster sterols, and it now appears that the sterol which had been tentatively named ostreasterol II: acetate, m.p. 104–105°, $[\alpha]_D$ −17.2° (15), was a mixture of cholesterol and cholestanol.

As a rule the sterols of bivalves form complex, difficulty separable mixtures of homologs and epimers of varying degrees of unsaturation, in which the diunsaturated C-21 epimers of the order C_{28} predominate. Occasionally one sterol may occur in considerable excess over the others, thereby facilitating its separation, as in the case of the original isolation of ostreasterol. In this connection the sterol isolated by Tsujimoto from the bivalve, *Tridacna gigas* (16c) is of particular interest. Larger amounts of starting material made possible a more extensive purification which eventually afforded shakosterol, m.p. 146–147°; acetate, m.p. 156–157°, which may possibly be identical with brassicasterol, m.p. 148°; acetate, m.p. 158°.

The data shown in Table VII demonstrate a surprising constancy of the fat content of the various fresh mollusks, and the amount of unsaponifiable matter present in the fats. The average fat content is somewhat higher in the gastropodes (snails) than in the pelecypodes (bivalves). Most outstanding is the fact that the high melting points of the sterylacetates from all pelecypodes indicate the absence of cholesterol as the principal sterol in these mollusks. In contrast, all gastropodes were found to contain cholesterol as their principal sterol. It must be emphasized, however, that these differences in sterol content are of quantitative rather than qualitative nature, since in some cases the presence of cholesterol has been detected in pelecypodes, and the presence in gastropodes of sterols other than cholesterol. Nevertheless the over-all difference is quite distinct and merits special attention. It had at first been assumed (15) that the difference in sterol content between a typical pelecypode such as the oyster, and a typical gastropode, such as *Fulgur*, is due to the exogeneous origin of sterols in mollusks. The herbivorous oyster was thought to assimilate the plant sterols of its phytoplancton diet, and the carnivorous marine snail to utilize the cholesterol of its diet. These assumptions had led to the formulation of the tentative hypothesis that invertebrates, and in particular marine invertebrates, are incapable of synthesizing sterols. Since then the results of studies on the sterols of echinoderms (2) and sponges (21) have discredited the value of this hypothesis. In equal disagreement with it are the data derived from studies on the sterols of gastropodes. These mollusks have been found to contain cholesterol as their principal sterol regardless of their feeding habits. Not only in the herbivorous land snails like *Helix* and *Arion*, (17) but also in the marine gastropode *Haliotis* (16), which feeds exclusively upon algae, has cholesterol been shown to be the major constituent of the sterol mixture. It appears therefore that the sterol content of mollusks is independent of their diet, and that the change from the cholesterol of the gastropodes to the "ostreasterol-like" compounds of the pelecypodes, or *vice versa*, marks a significant evolutionary step.

SUMMARY

A system for the classification of C-24 epimeric sterols has been proposed.

The contributions of C-24 substituents to the molecular rotation of sterols has been discussed.

Evidence has been given which indicates that stigmasterol and poriferasterol, and β-sitosterol and clionasterol are C-24 epimers.

It has been shown that the ergostanol and stigmastanol series have similar configurations at C-24.

The sterols of mollusks have been discussed, and the suggestion has been made that ostreasterol is identical with chalinasterol, and shakosterol with brassicasterol.

Attention has been called to the significant differences in sterol content between the pelecypodes (bivalves) and gastropodes (snails).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

THE WILLGERODT REACTION. V. SUBSTITUTED ACETAMIDES FROM β-SUBSTITUTED ACRYLIC ACIDS[1]

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It has recently been shown that the Willgerodt reaction is not limited to use with aryl alkyl ketones but serves also for the conversion of acetylenes ($RC\equiv CH$, $RC\equiv CCH_3$) (2, 3) into carbonamides retaining the same carbon skeleton as the starting compounds (RCH_2CONH_2 and $RCH_2CH_2CONH_2$, respectively). Similarly, it has been demonstrated that olefins of the types $RCH{=}CH_2$ and $RCH{=}CH(CH_2)_nCH_3$ (3, 4, 5, 6), secondary carbinols of the types $RCHOHCH_3$ and $RCHOH(CH_2)_nCH_3$ (6), completely aliphatic ketones of the types $RCO(CH_2)_nCH_3$ (1, 6b) and mercaptans of the general structure $RCHSH(CH_2)_nH$ (6b) are converted by the action of hot ammonium polysulfide or ammonium hydroxide-sulfur mixtures into carbonamides with loss of the original functional group but with the retention of the relative arrangement of carbon atoms in the starting compound.

Undecylenic acid, the only olefinic acid previously reported (4) to have been studied under the conditions of the Willgerodt reaction, reacted normally without loss of carbon atoms and yielded a mixture of the mono- and di-amides of nonane-1,9-dicarboxylic acid, which gave pure nonane-1,9-dicarboxylic acid upon hydrolysis:

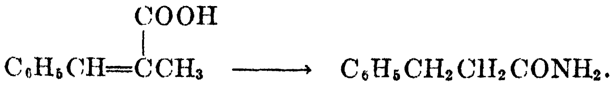
$$CH_2{=}CH(CH_2)_8COOH \rightarrow \text{(mixture of amides)} \rightarrow HOOC(CH_2)_9COOH.$$

We have now extended our investigation to include α,β-unsaturated acids and have found that they react smoothly to form carbonamides having one less carbon atom than the starting acid. The carboxyl group is lost but the product otherwise retains the carbon skeleton of the original compound.

Thus, cinnamic acid gave 76.7% of phenylacetamide when it was heated with a mixture of concentrated aqueous ammonia, sulfur, and dioxane.

$$C_6H_5CH{=}CHCOOH \rightarrow C_6H_5CH_2CONH_2$$

In the one example studied in which the aliphatic carbon chain was branched *viz.*, *trans*-α-methylcinnamic acid, the carboxyl group was eliminated from a penultimate position and the straight chain β-phenylpropionamide was formed:



$$C_6H_5CH{=}\overset{\displaystyle COOH}{\overset{|}{C}}CH_3 \longrightarrow C_6H_5CH_2CH_2CONH_2.$$

This reaction suggests a close analogy to the conversion of 1-phenylpropene into β-phenylpropionamide under similar conditions (3).

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[1] For previous papers of this series, see References 1–4.

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2-Nonenoic acid, chosen as an example of a completely aliphatic β-substituted acrylic acid, gave *n*-caprylamide:

$$CH_3(CH_2)_5CH{=}CHCOOH \rightarrow CH_3(CH_2)_6CONH_2$$

The yields of amides from the acids of the type $RCH{=}CHCOOH$ were higher and the crude reaction products appeared to be cleaner than those obtained from the corresponding olefins ($RCH{=}CH_2$) in previous investigations carried out in this Laboratory (3, 4).

The interesting cleavage of 9-propionylanthracene to give a high yield of anthracene under conditions of the Willgerodt reaction (2) prompted the investigation of β-(9-anthracene)acrylic acid under similar reaction conditions. This unsaturated acid did not yield β-(9-anthracene)acetamide but, like 9-propionylanthracene, was cleaved to anthracene. The β-(9-anthracene)-acrylic acid was synthesized from 9-anthraldehyde and malonic acid by the Doebner method.

EXPERIMENTAL

Phenylacetamide from cinnamic acid A mixture of 4.0 g. of cinnamic acid, 8.8 ml. of concentrated (15 *M*) aqueous ammonia, 5.6 g. of sulfur, and 8 ml. of dioxane was heated in a sealed glass tube at 170 ± 5° for five and one-half hours. When the mixture had cooled to room temperature, the supernatant liquid was decanted from the crystals of nearly pure amide, which were then washed with ammonium sulfide solution and recrystallized from water to give 1.36 g. of colorless phenylacetamide, m.p. 159–160° cor. The mother liquor from the reaction mixture was evaporated to dryness and the remaining amide was extracted from the residue with hot water, giving an additional 1.40 g. of phenylacetamide, m.p. 158–159°; total yield, 76.7%. The identity of the product was confirmed by direct comparison with an authentic specimen.

β-Phenylpropionamide from α-methylcinnamic acid. *trans*-α-Methylcinnamic acid was prepared by the method of Perkin (7). A mixture of 4.0 g. of the *trans*-α-methylcinnamic acid, 8.8 ml. of concentrated aqueous ammonia, 5.6 g. of sulfur, and 8.0 ml. of pyridine was heated in a sealed glass tube at 170 ± 5° for five and one-half hours. The reaction mixture was evaporated to dryness and the product extracted thoroughly with hot water. From the clarified extracts β-phenylpropionamide separated as colorless needles, yield, 2.31 g. (63%), m.p. 98–99° cor. One recrystallization from water (Norit) yielded 2.00 g., m.p. 101–102° cor., not depressed by admixture with an authentic specimen of β-phenylpropionamide (m.p. 100–101.5°).

n-Caprylamide from 2-nonenoic acid. 2-Nonenoic acid was prepared according to the procedure of Zaar (8). A mixture of 4.0 g. of 2-nonenoic acid, 8.8 ml. of concentrated aqueous ammonia, 5.6 g. of sulfur, and 8.0 ml. of pyridine was heated in a sealed glass tube at 160 ±5° for four and one-half hours. The contents of the tube were evaporated to dryness and extracted with ether to remove the amide. The dark, waxy solid from the ether was recrystallized from 50% alcohol (Norit) to give 2.46 g. (69%) of slightly impure amide. A second recrystallization from 50% alcohol gave 1.49 g. (41%), m.p. 102.5–103.5°. After another recrystallization, from ligroin, the amide was obtained as 1.23 g. of shining plates, m.p. 104–105° cor.; the melting point has been reported as 105° (9) and 106° (10). The amide was hydrolyzed to the acid in boiling glacial acetic acid-hydrochloric acid, and the acid was converted into the anilide, which melted, after recrystallization from 50% alcohol, at 51.5–52°; the reported m.p. is 55° (9).

β-(9-Anthracene)acrylic acid. A mixture of 2.06 g. of 9-anthraldehyde (11, 12), 1.4 g. of malonic acid, 0.5 ml. of piperidine, and 3.0 ml. of pyridine was heated on the steam-bath for four hours; the solution was then refluxed for one hour in an oil-bath at 125–130°. The mixture was cooled, diluted with 20 ml. of water, and acidified with dilute hydrochloric acid. The orange oil which separated soon solidified. The orange solid weighed 3.08 g. when dry and began to melt with decomposition at about 145°; it evidently consisted largely of the substituted malonic acid. The material was heated for thirty minutes at 180–190° to eliminate carbon dioxide. The dark red melt solidified on cooling and was purified by recrystallization from 12 ml. of chlorobenzene containing 0.5 ml. of glacial acetic acid. β-(9-Anthracene)acrylic acid formed bright yellow needles, m.p. 235.5–237.5° (dec.); yield, 2.05 g. (82.6%). A second recrystallization gave a first crop of 1.80 g., m.p. 246–247° (dec.). The analytical sample was recrystallized once from acetone-ethyl acetate.

Anal. Calc'd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87.

Found[3]: C, 82.12; H, 4.96.

Cleavage of β-(9-anthracene)acrylic acid under Willgerodt conditions. A mixture of 0.60 g. of β-(9-anthracene)acrylic acid, 1.3 ml. of concentrated aqueous ammonia, 0.84 g. of sulfur, and 1.2 ml. of dioxane was heated in a sealed glass tube at 170 ± 5° for five and one-half hours. The reaction mixture was evaporated to dryness and the dry residue extracted with boiling glacial acetic acid. The only crystalline material isolated from the acetic acid after clarification with Norit was anthracene in 50% yield. The anthracene, after recrystallization from chlorobenzene, consisted of yellow plates, m.p. 215–216° cor.; the melting point was not depressed by admixture with pure anthracene, m.p. 216–217° cor.

SUMMARY

Cinnamic acid gave phenylacetamide under the conditions of the Willgerodt reaction. *trans*-α-Methylcinnamic acid yielded β-phenylpropionamide, and 2-nonenoic acid yielded *n*-caprylamide. β-(9-Anthracene)acrylic acid was cleaved to anthracene in a manner similar to 9-propionylanthracene.

PHILADELPHIA, PA.

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[3] Analysis by Mr. John F. Dowdall.

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

REACTIONS OF VANILLIN AND ITS DERIVED COMPOUNDS. III.[1] THE CANNIZZARO REACTION OF VANILLIN[2]

IRWIN A. PEARL

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It has been a generally accepted fact that *ortho*- and *para*-hydroxybenzaldehydes, whether further substituted or not, are not amenable to the Cannizzaro reaction (1). Vanillin has been found to be no exception (2–5). In the first paper of this series it was demonstrated that vanillin underwent a Cannizzaro reaction with alkali in the presence of silver oxide to form vanillic acid and vanillyl alcohol, the latter in the form of its condensation product, 4,4′-dihydroxy-3,3′-dimethoxydiphenylmethane, and the former in an amount greater than 50% equivalent to the silver oxide present (6). All these reactions were accompanied by the simultaneous reduction of the silver oxide to a fluffy, porous metallic silver, and it was suspected that the metallic silver was the catalyst for the Cannizzaro reaction. The present paper pertains to a study of the reaction of vanillin with alkali in the presence of active silver metal (7).

Boiling for one hour of a solution of vanillin in excess 15% sodium hydroxide in the presence of 100 mole-% of dry fluffy silver (prepared by reducing silver oxide with vanillin and alkali, and having an apparent specific gravity of 0.90[3]) resulted in a quantitative Cannizzaro reaction with the formation of vanillic acid and polymerized vanillyl alcohol[4] in equivalent amounts. The same reaction in the presence of only 2 mole-% of the same silver yielded 19% of Cannizzaro reaction products and 80% of recovered vanillin, indicating that more silver surface was probably necessary for completion of the reaction in the 1-hour reaction time.

The effect of the type of silver metal upon the reaction was studied. A number of samples of silver metal having different apparent specific gravities and surface characteristics were prepared and tested under identical conditions

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[1] For paper II of this series see Pearl, *J. Am. Chem. Soc.*, **68**, 1100 (1946).

[2] This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Committee on Waste Disposal and conducted for the Committee by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the Committee to publish these results.

[3] The apparent specific gravity of the silver powder was obtained by tightly packing a 5-ml. volumetric cylinder with the powder and noting the weight. For those silver metals which could not be dried without fusion, the wet metal was packed into the volumetric cylinder and then quantitatively washed onto a tared sintered crucible and dried at 105°.

[4] It is recognized that the use of the term "polymerized vanillyl alcohol" for this product is not strictly correct according to the classical definition of "polymer," but the product does fall within the scope of the definition of "condensation polymer" (as distinguished from "association polymer") as used by Carothers [*J. Am. Chem. Soc.*, **51**, 2548 (1929)]. For want of a better term, "polymerized vanillyl alcohol" in this paper will refer to the alcohol product in various stages of polymerization (or polycondensation) as isolated from the reaction mixtures.

(as outlined above) as Cannizzaro reaction catalysts. Comparative results are shown in Table I.

The relationship of apparent specific gravity to the percentage of Cannizzaro reaction, together with the negative results obtained with the metallurgical types of silver, indicates that a large surface area is the requisite of a Cannizzaro reaction silver catalyst, the source of the finely divided silver having little effect. It appeared evident, therefore, that silver metals having apparent specific gravities less than 0.90 would catalyze the complete Cannizzaro reaction of vanillin either in a shorter reaction period or with a smaller silver-vanillin ratio. This proved to be the case.

TABLE I

EFFECT OF TYPE OF SILVER ON CANNIZZARO REACTION OF VANILLIN

SOURCE OF SILVER USED	APPARENT SP. GR.	VANILLIC ACID, %	POLYMERIZED VANILLYL ALCOHOL, %	RECOVERED VANILLIN, %
Granular metallurgical	10.5	0	0	98.3
Heating of silver oxide	4.7	0	0	97.8
Reduction of silver nitrate with ferrous sulfate	1.56	16.6	14.3	71.1
Vanillic acid process—cold (6)	0.98	23.7	23.0	49.2
Vanillic acid process—hot (6)	0.90	50.0	50.0	0

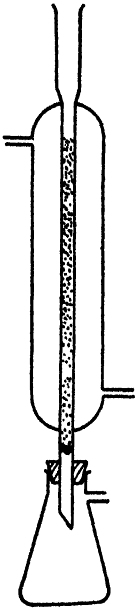


FIG. 1. APPARATUS FOR CANNIZZARO REACTION

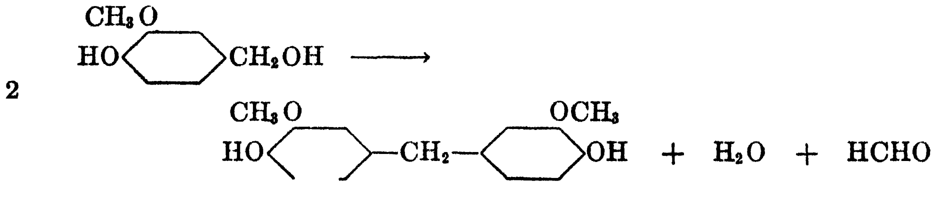
The very fluffy silver obtained on oxidation of vanillin with alkali and silver nitrate (8) caused complete reaction to take place in a few minutes at low temperatures and with low silver-vanillin ratios. The Cannizzaro reaction of vanillin with this freshly prepared catalyst always yielded an excess of vanillic acid over that called for by theory. This was due to the small amount of silver oxide present in the silver catalyst caused by oxidation with the sodium nitrate present in the reaction mixture (8). The silver catalyst did not lose its activity with reuse, and all succeeding experiments yielded vanillic acid and polymerized vanillyl alcohol in equivalent amounts.

The activity and stability of this fluffy silver made it ideal for use in a continuous Cannizzaro process. Passage of a hot dilute alkaline solution of vanillin over the heated catalyst in the apparatus pictured in Figure 1 resulted in a quantitative Cannizzaro reaction in as short a contact time as one minute. Catalysts with higher apparent specific gravities gave the desired results with longer contact times.

After it was found that vanillin would undergo the ordinary Cannizzaro reaction in the presence of active silver, the possible reduction of vanillin to vanillyl alcohol by means of the crossed Cannizzaro reaction with formaldehyde in the presence of silver was investigated. Davidson and Bogert (9) have proposed general directions for carrying out the crossed Cannizzaro reaction of aromatic aldehydes, in which the aldehyde is treated with 1.3 moles of formalin and excess alkali in methanolic solution. Addition of a mixture of vanillin and 1.3 moles of formalin to a stirred aqueous mixture of sodium hydroxide and active silver and boiling of the resulting mixture under reflux for 0.5 hour yielded only polymerized vanillyl alcohol and no vanillic acid. If the vanillin is dissolved in water containing one mole of alkali, treated with silver and 1.3 moles of formalin, and then with excess alkali, a substantial amount of vanillic acid is obtained in addition to the polymerized vanillyl alcohol.

The appearance of vanillic acid in the last experiment but not in the first indicated that an ordinary Cannizzaro reaction of vanillin might have taken place before addition of the formalin in the presence of active silver and only one mole of sodium hydroxide. This was confirmed by an experiment in which a solution of vanillin in water containing one mole of sodium hydroxide (enough to form the sodium salt) was treated with active silver; this yielded 30% of Cannizzaro reaction products.

The crossed Cannizzaro reaction of vanillin in the presence of silver with a formaldehyde-vanillin ratio of 5 to 1 yielded 82.5% of uncondensed vanillyl alcohol. This was the only experiment in the whole study which yielded vanillyl alcohol in an unpolymerized form. In the case of the crossed Cannizzaro reaction of vanillin, the following reaction also operates (6). Although this reaction



is not reversible, it is evident that a large excess of formaldehyde actually prevents the reaction from taking place.

All attempts to obtain a crossed Cannizzaro reaction without the silver catalyst failed completely.

EXPERIMENTAL

All melting points given are uncorrected.

Reaction of vanillin with alkali in presence of active silver. A suspension of 21.6 g. (0.2 atom) of dried fluffy silver metal [from vanillin oxidation with silver oxide and alkali (6)], having an apparent specific gravity of 0.90, in 250 cc. of water was treated successively with 40 g. (1.0 mole) of sodium hydroxide and 30.5 g. (0.2 mole) of vanillin. The mixture was heated to boiling under reflux for one hour, filtered, and the silver was thoroughly washed with water. The cooled filtrate and washings were acidified with carbon dioxide and extracted with ether. The ether was dried and distilled to yield 13.3 g. (50%) of a yellow resinous solid which was recrystallized from water to give white needles of 4,4′-dihydroxy-3,3′-dimethoxydiphenylmethane, melting at 108–109° and not lowering a mixed melting point with authentic 4,4′-dihydroxy-3,3′-dimethoxydiphenylmethane. In addition, some uncrystallizable resinous polymeric material was obtained. The aqueous carbonated layer was acidified with dilute sulfuric acid and extracted with ether. This yielded 16.8 g. (50%) of vanillic acid which, upon recrystallization from water, melted at 210–211°. An alternate method gave substantially identical results. The original filtrate and washings were acidified with sulfur dioxide and extracted with ether. The ether was extracted with 8% sodium bicarbonate solution, dried and distilled to give the polymerized vanillyl alcohol product, part of which could be recrystallized from water to give the dihydroxydimethoxydiphenylmethane. Acidification and ether extraction of the bicarbonate extract yielded vanillic acid.

The above reaction was repeated in the presence of only 2 mole-% of the same silver catalyst. Yields of 9.6% vanillic acid, 9.5% polymerized vanillyl alcohol, and 80% recovered vanillin were obtained.

Effect of type of silver on Cannizzaro reaction of vanillin. The following metallic silvers were prepared and used in the experiment outlined above. Results are given in Table I.

Granular metallurgical silver was screened to pass a 10-mesh sieve. The apparent specific gravity was 10.5.

Finely divided silver was prepared by heating silver oxide. The latter was formed by treating a solution of 34 g. of silver nitrate with an aqueous solution of 8 g. of sodium hydroxide. The precipitated oxide was filtered, washed free of nitrate with water and dried at 110°. The oven-dried oxide was then heated above 300°, when the brownish black oxide changed to a white shiny metal. The granular metal was suspended in water and mixed in a Waring Blendor for several minutes. The very fine white powder of pure silver obtained had an apparent specific gravity of 4.7.

Finely divided silver having an apparent specific gravity of 1.56 was prepared by treating a boiling solution of 34 g. of silver nitrate in 125 cc. of water with ferrous sulfate solution until all the brown precipitate which formed redissolved. The silver was deposited as a gray, finely divided precipitate; this was filtered, washed with dilute hydrochloric acid, then with water, and dried at 110°.

Two fluffy silver metals were prepared by adding vanillin to aqueous alkaline suspensions of silver oxide at 55° and at 35° as described in an earlier paper (6). These silver metals had apparent specific gravities of 0.98 and 0.90, respectively.

Reaction of vanillin with alkali in presence of very active silver. The wet spongy silver (43.2 g.) (0.4 atom), formed by adding a solution of 0.4 mole of silver nitrate to an alkaline solution of vanillin at 55° (8) and having an apparent specific gravity of 0.2, was covered with 800 cc. of water and treated with 96 g. (2.4 moles) of sodium hydroxide. The mixture was cooled to 30° and 60.8 g. (0.4 mole) of vanillin was added. The temperature rose to 38°. After 10 minutes the mixture was filtered and the silver was washed thoroughly with water and stored under water. The filtrate and washings were acidified with sulfur dioxide and worked up as described above. Yields of 40.2 g. (59.8%) of vanillic acid and 20 g. (37.8%) of polymerized vanillyl alcohol were obtained.

The spongy silver obtained in this experiment was employed in another identical experiment, but the yields were 33.4 g. (49.6%) of vanillic acid and 25.3 g. (47.6%) of polymerized vanillyl alcohol.

This reused spongy silver also catalyzed substantially quantitative Cannizzaro reactions of vanillin with silver-vanillin mole ratios of one to ten in 15 minutes.

Continuous Cannizzaro reaction of vanillin. A reaction column was prepared from a 30-cm. Pyrex Liebig condenser. A constriction was made two inches from the lower end and a plug of steel wool was inserted through the top. The column was packed with wet active spongy silver (apparent specific gravity, 0.17) and steam was circulated through the condenser jacket. A filter flask was used as a receiver. A hot solution of 30.4 g. (0.2 mole) of vanillin and 48 g. (1.2 moles) of sodium hydroxide in one liter of water was slowly added at the top of the column. The receiving flask was connected to the water-pump and a slight vacuum was applied. The vacuum was adjusted so that the alkaline vanillin solution was in contact with the catalyst for approximately one minute. After all the solution had passed, the column was washed with water. The percolate and washings were acidified with sulfur dioxide and extracted with ether. The ether was dried and distilled, leaving a mixture of white crystals and yellow solid which was then shaken with 8% sodium bicarbonate solution and filtered. The precipitate of polymerized vanillyl alcohol (melting at 95–100°) weighed 13 g (46.9%). The sodium bicarbonate solution was acidified with dilute sulfuric acid giving a white granular precipitate. The mixture was extracted with ether and worked up as before to yield 16.8 g. (50%) of vanillic acid melting at 207–210°.

This experiment was repeated many times with the same catalyst and the catalyst did not lose any of its activity.

Active silver catalysts, prepared by the silver oxide process at 55° (6) and having apparent specific gravities of approximately 0.90, could be used in the continuous process, but contact times of about 10–20 minutes were necessary for complete transformation of the vanillin.

Crossed Cannizzaro reaction of vanillin. A stirred suspension of 21.6 g. (0.2 atom) of spongy silver, having an apparent specific gravity of 0.17, in a solution of 48 g. (1.2 moles) of sodium hydroxide in 450 cc. of water at 40° was treated with a thin paste of 30.4 g. (0.2 mole) of vanillin, 20.0 cc. (0.26 mole) of 37% formalin, and 50 cc. of water. The resulting mixture was gradually heated to boiling under reflux and mercury-sealed stirring and refluxed for 30 minutes. After cooling, the mixture was filtered and the silver was washed well with water. The filtrate and washings were saturated with carbon dioxide, then saturated with sodium chloride and extracted with ether. The ether was dried and distilled to yield 25.5 g. (96.2%) of polymerized vanillyl alcohol as a light yellow resin. Recrystallization of this material from ligroin or water yielded white crystalline products with indefinite melting points ranging from 65–110°. No vanillic acid could be found in the carbonated solution.

The same reactants were employed in an entirely different reaction procedure. A solution of 0.2 mole of vanillin and 0.2 mole of sodium hydroxide in 450 cc. of water was first treated with 0.2 atom of silver (from the last experiment) and then with 0.26 mole of formalin. One mole of solid sodium hydroxide was added with vigorous stirring and the mixture was heated to boiling under reflux as above. The reaction mixture was worked up in the same manner as the last experiment. Yields of 8.8 g. (26%) of vanillic acid and 18.7 g. (71%) of polymerized vanillyl alcohol, were obtained.

Crossed Cannizzaro reaction of vanillin with large excess of formaldehyde. A mixture of 21.6 g. (0.2 atom) of active silver (from the last experiment), 100 cc. of water, and 24.0 g. (0.6 mole) of sodium hydroxide was blended in a Waring Blendor. The temperature of the mixture at this point was approximately 45–50°. Without agitation, a mixture of 15.2 g (0.1 mole) of vanillin and 50 cc. (0.5 mole) of 37% formalin was added and the Blendor was turned on. The temperature rose gradually until after 30 minutes it reached 85°, where the silver suddenly became light colored and very heavy. The mixture was filtered and the silver washed with water. The silver was hard and had an apparent specific gravity of 4.1. The combined filtrate and washings were saturated with carbon dioxide and sodium chloride and then extracted with ether. The ether solution was dried and distilled, leaving 12.7 g. of light yellow oil which crystallized on standing to white prisms melting at 105–112°. Recrystallization from benzene gave needles melting at 114–115° and not depressing the m p. of a mixture with authentic vanillyl alcohol. The yield was 82.5%. Acidification of the carbonated aqueous layer and subsequent ether extraction yielded a little more vanillyl alcohol and 1.2 g. (7.1%) of vanillic acid melting at 209–210°.

SUMMARY

Active silver metal catalyzes the quantitative Cannizarro reaction of vanillin, to yield equivalent amounts of vanillic acid and polymerized vanillyl alcohol. Active silver also catalyzes the crossed Cannizzaro reaction of vanillin with formaldehyde to yield only polymerized vanillyl alcohol. A crossed Cannizzaro reaction with excess formaldehyde yields unpolymerized vanillyl alcohol.

APPLETON, WIS.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

SILVER CATALYZED REACTIONS OF PHENOLIC ALDEHYDES[1]

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In previous papers the quantitative oxidation of vanillin to vanillic acid with alkali and one-half mole of silver oxide (1, 2) and the Cannizzaro reaction of vanillin in the presence of metallic silver (3) were reported. In order to determine whether these reactions were characteristic of vanillin alone or could be applied to other aldehydes which fail to undergo the Cannizzaro reaction under ordinary conditions (4), the study reported herein was initiated (5). This paper presents a number of experiments on other *o*-and *p*-hydroxybenzaldehydes. The compounds studied were *o*-vanillin, 5-chlorovanillin, salicylaldehyde, and *p*-hydroxybenzaldehyde. In addition *p*-dimethylaminobenzaldehyde, which heretofore could not be made to undergo the Cannizzaro reaction (6, 7), was investigated.

Reaction of *o*-vanillin (2-hydroxy-3-methoxybenzaldehyde) with 0.5 mole of silver oxide and excess alkali gave an almost quantitative yield of *o*-vanillic acid. Like its *p*-analog, *o*-vanillin had never been oxidized in good yield directly to *o*-vanillic acid. Rupp and Linck (8) succeeded in obtaining high yields of *o*-vanillic acid from *o*-vanillin by heating with potassium hydroxide at 215°.

5-Chlorovanillin was easily oxidized with alkali and 0.5 mole of silver oxide to the corresponding acid. When the silver oxide-vanillin ratio was reduced further, 5-chlorovanillyl alcohol appeared in the theoretical amount calculated on the basis of a Cannizzaro reaction (1). Reaction of 5-chlorovanillin with alkali in the presence of active silver metal gave equivalent amounts of acid and alcohol, and the crossed Cannizzaro reaction of 5-chlorovanillin with formaldehyde in the presence of active silver yielded only 5-chlorovanillyl alcohol. Salicylaldehyde acted in exactly the same manner as did 5-chlorovanillin. In all Cannizzaro experiments with these two aldehydes, the alcohols were isolated in their uncondensed state, thus acting differently from vanillyl alcohol under the same conditions (1, 3).

p-Hydroxybenzaldehyde was easily oxidized with alkali and 0.5 mole of silver oxide to *p*-hydroxybenzoic acid, and readily underwent the regular and crossed Cannizzaro reactions in the presence of active silver. In the latter reactions, acidification of the filtered reaction mixtures with strong acids yielded *p*-hydroxybenzyl alcohol in a polycondensed form, but acidification with a weak acid, such as carbon dioxide, gave the uncondensed *p*-hydroxybenzyl alcohol. Analogous reactions of vanillin gave the polycondensed alcohol under all acidification conditions, except in the presence of a large excess of formaldehyde (1, 3).

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[1] This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Committee on Waste Disposal and conducted for the Committee by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the Committee to publish these results.

Dismutation of *p*-dimethylaminobenzaldehyde by means of the Cannizzaro reaction took place with ease in the presence of active silver to yield equivalent amounts of *p*-dimethylaminobenzoic acid and *p*-dimethylaminobenzyl alcohol. This was the only aminobenzaldehyde studied, but the results obtained indicate that active metallic silver will probably catalyze the Cannizzaro reaction of all *o*- and *p*-hydroxy, amino, and substituted aminobenzaldehydes which are unaffected by alkali alone.

In the above experiments, if the active silver used was prepared by reduction with the aldehyde of silver oxide prepared *in situ* from alkali and silver nitrate (Process II), the yields of the acid in the Cannizzaro reactions were always greater than 50%. This is more evidence that some of the active silver metal produced in the aldehyde oxidation reaction is reoxidized to silver oxide by the nitrates present in the reaction mixture. Reuse of the active silver always gave equivalent amounts of acid and alcohol.

The oxidation of aldehydes ordinarily not amenable to the Cannizzaro reaction, by means of alkali and 0.5 mole of silver oxide, affords a simple laboratory method for the preparation of the corresponding acids. This is especially true in those instances in which the aldehyde is readily available, *e.g.*, vanillin and *o*-vanillin.

All the above reactions employing catalytic silver were repeated without the use of silver and in none of the latter cases did reaction take place, the aldehyde being recovered in all instances.

EXPERIMENTAL

All melting points given are uncorrected.

Starting materials. *o*-Vanillin (2-hydroxy-3-methoxybenzaldehyde) was a commercial technical product furnished by Monsanto Chemical Company. It was used without further purification.

5-Chlorovanillin was prepared by the method of Menke and Bentley (9) and was obtained as white crystals melting at 164–165°.

The other aldehydes used were Eastman Kodak Company products and were used without further purification.

To avoid repetition, details have been given for representative reactions. Analogous reactions discussed above and given in Table I were carried out by the following methods with slight variations required in individual cases.

Reaction of o-vanillin with alkali and 0.5 mole of silver oxide (Process I). Silver oxide was freshly prepared by mixing 25% solutions of 307 g. (1.8 moles) of silver nitrate and 75 g. (1.8 moles) of sodium hydroxide, allowing to settle, and decanting the supernatant liquor. The oxide was filtered, washed well with water, transferred to a 6-liter beaker, and covered with 3000 cc. of water. With vigorous stirring the silver oxide suspension was treated with 362 g. (9 moles) of sodium hydroxide. The temperature at this point was 40°. With continued stirring 275 g. (1.8 moles) of *o*-vanillin was added at one time. A very vigorous reaction set in and the temperature rose to 80°. Stirring was continued until the temperature dropped to 50°, and then the reaction mixture was allowed to settle. The fluffy precipitated silver was filtered and washed with water. The combined filtrate and washings were acidified with dilute sulfuric acid and cooled. The white crystals which separated were filtered, washed with water, and dried; the yield was 269 g. (89.1%) of *o*-vanillic acid melting at 150–152°. Extraction of the filtrate with ether yielded an additional 13.3 g. (4.4%) of *o*-vanillic acid as a white solid which was recrystallized from water to give white crystals melting at 151–152°.

Reaction of p-hydroxybenzaldehyde with alkali and silver nitrate (Process II). To a well-stirred solution of 48.0 g. (1.2 moles) of sodium hydroxide and 24.4 g. (0.2 mole) of *p*-hydroxybenzaldehyde in 400 cc. of water at 50° was added 34.0 g. (0.2 mole) of silver nitrate in 50 cc. of water. An immediate reaction took place and the temperature rose considerably. The mixture was stirred for 30 minutes without heating and filtered. The precipitated spongy silver was washed with water and stored under water. The combined filtrate and washings were acidified with sulfur dioxide [use of nonreducing acids in this case gives nitro compounds (2)] to give 25.0 g. (90.6%) of *p*-hydroxybenzoic acid melting at 212–213°. The aqueous filtrate, upon saturating with sodium chloride and extracting with ether, yielded an additional 2.6 g. (9.4%) of *p*-hydroxybenzoic acid melting at 207–209° which, upon crystallization from water, melted at 212–213°.

Reaction of 5-chlorovanillin with alkali and less than 0.5 mole of silver oxide. Freshly prepared silver oxide (0.025 mole) was prepared in the usual manner from 8.25 g. of silver nitrate and 2.1 g. of sodium hydroxide. The filtered and washed oxide was covered with 800 cc. of water and treated with stirring with 40 g. (1.0 mole) of sodium hydroxide. This stirred suspension was heated to 60° and treated with 46.5 g. (0.25 mole) of 5-chlorovanillin, which caused reaction to set in and the temperature to rise. The mixture was heated to boiling under reflux with stirring for 30 minutes, filtered, and the silver precipitate was washed with water. The combined filtrate and washings were acidified with carbon dioxide until acid to phenolphthalein and extracted with ether. The ether was dried with sodium sulfate and distilled, leaving 18.1 g. (38.4%) 5-chlorovanillyl alcohol as a white powder melting at 95–97°. Repeated recrystallizations from petroleum ether or water gave white needles melting at 110–111°.

Anal. Calc'd for $C_8H_9ClO_3$: CH_3O, 16.45. Found: CH_3O, 16.49.

The carbonated aqueous solution was acidified further with sulfur dioxide The white crystalline precipitate was filtered, washed with water and dried to give 29.4 g. (58.1%) of 5-chlorovanillic acid melting at 242–244°. Recrystallization from dilute acetic acid raised the melting point to 244–245°.

Extraction of the sulfur dioxide-saturated filtrate with ether yielded an additional 1.4 g. (3.0%) of 5-chlorovanillyl alcohol which, upon recrystallization from water, melted at 110–111°.

Reaction of p-hydroxybenzaldehyde with alkali in the presence of active silver. A mixture of 24.4 g. (0.2 mole) of *p*-hydroxybenzaldehyde, 48.0 g. (1.2 moles) of sodium hydroxide, 21.6 g. (0.2 atom) of active silver metal (from the reduction of silver oxide with *p*-hydroxybenzaldehyde by Process I), and 400 cc. of water was heated to boiling for 1 hour and allowed to cool The mixture was filtered and the silver was washed with water. The combined cooled filtrate and washings were saturated with carbon dioxide and sodium chloride and extracted with ether. The ether was dried and distilled under reduced pressure to give 11.7 g. (47.1%) of *p*-hydroxybenzyl alcohol as a white solid melting at 123–124°. Recrystallization from water yielded white crystals, m.p. 124–125°. The carbonated aqueous solution was further acidified with sulfur dioxide and extracted with ether to yield 13.0 g. (49.6%) of *p*-hydroxybenzoic acid as white platelets melting at 208–210° which, upon recrystallization from water, melted at 212–213°.

In an alternate method the filtered alkaline reaction mixture was acidified directly with sulfur dioxide, saturated with sodium chloride, and extracted with ether. The ether was dried and distilled. The residue was treated with excess 8% sodium bicarbonate solution and filtered. The precipitate, weighing 10.6 g. (43.0%), was a resinous condensed *p*-hydroxybenzyl alcohol and was insoluble in boiling water or benzene. Acidification of the bicarbonate solution yielded 13.0 g. (49.6%) of *p*-hydroxybenzoic acid melting at 208–210° which, upon recrystallization from water, melted at 212–213°.

Reaction of salicylaldehyde with alkali and formaldehyde in the presence of active silver. To a vigorously agitated suspension of 10.8 g. (0.1 atom) of fluffy active silver (prepared by the reduction of silver oxide with salicylaldehyde) in 100 cc. of water was added 24.0 g.

(0.6 mole) of solid sodium hydroxide. The temperature at this point was 53°. A mixture of 12.2 g. (0.1 mole) of salicylaldehyde and 50 cc. (0.5 mole) of 37% formalin was then added with continued agitation. Violent reaction set in and the temperature rose to 90°. After 30 minutes of agitation, the mixture was heated to boiling, allowed to cool, and filtered. The filtrate and washings were saturated with carbon dioxide and with sodium chloride and extracted with ether. The ether was dried and distilled under reduced pressure, yielding 12.2 g. (98.4%) of salicyl alcohol as white crystals melting at 83–85°. Recrystallization from petroleum ether raised the melting point to 85–86°.

TABLE I

SILVER CATALYZED REACTIONS

ALDEHYDE	SILVER OXIDE (MOLE)	SILVER (ATOM)	FORMALDEHYDE (MOLES)	ACID, %	ALCOHOL, %
o-Vanillin[a]	0.5[b]			93.5	
o-Vanillin	.5[c]			93.8	
5-Chlorovanillin	.5[b]			97.8	
5-Chlorovanillin	.5[c]			97.0	
5-Chlorovanillin	.1			58.1	41.4
5-Chlorovanillin		1.0[d]		49.0	48.1
5-Chlorovanillin		1.0[f]	5.0		98.4
Salicylaldehyde	.5[b]			98.6	
Salicylaldehyde	.5[c]			99.0	
Salicylaldehyde		1.0[d]		50.0	49.2
Salicylaldehyde		1.0[e]		61.6	36.7
Salicylaldehyde[a]		1.0[f]	5.0		98.4
p-Hydroxybenzaldehyde	.5[b]			98.9	
p-Hydroxybenzaldehyde[a]	.5[c]			100.0	
p-Hydroxybenzaldehyde[a]		1.0[d,f]		49.6	47.1[g]
p-Hydroxybenzaldehyde[a]		1.0[d,f]		49.6	43.0[h]
p-Hydroxybenzaldehyde		1.0[e]		69.3	26.8[g]
p-Hydroxybenzaldehyde		1.0[f]	5.0		97.2[g]
p-Hydroxybenzaldehyde		1.0[f]	5.0		92.8[h]
p-Dimethylaminobenzaldehyde		1.0[i]		43.6	44.5[j]

[a] Details in Experimental part.

[b] Silver oxide prepared according to Process I.

[c] Silver oxide prepared *in situ* according to Process II.

[d] Silver isolated from reaction of corresponding aldehyde according to Process I.

[e] Silver isolated from reaction of corresponding aldehyde according to Process II.

[f] Reuse of silver isolated from reaction of corresponding aldehyde according to Process II.

[g] *p*-Hydroxybenzyl alcohol, m.p. 124–125°.

[h] Resinous *p*-hydroxybenzyl alcohol calculated as *p*-hydroxybenzyl alcohol.

[i] Silver prepared by reduction of silver oxide by vanillin according to Process I.

[j] *p*-Dimethylaminobenzyl alcohol was not isolated pure but the crude product was treated with methyl iodide in acetone to give dimethylaminobenzyl alcohol methiodide, m.p. 231–232° (6).

All compounds listed in Table I, except 5-chlorovanillyl alcohol, have been previously prepared and recorded. In all instances the melting points and properties of the compounds isolated in this study concurred with those in the literature.

SUMMARY

Four *o*- and *p*-hydroxy- and one amino-substituted benzaldehydes were subjected to reaction with alkali in the presence of either silver oxide or active silver metal. The reactions previously found to take place with vanillin also took place with these aldehydes.

Cannizzaro and crossed Cannizzaro reactions of *p*-hydroxybenzaldehyde yielded either crystalline or resinous *p*-hydroxybenzyl alcohol, depending upon the experimental procedure.

Active silver appears to be a universal catalyst for catalyzing the Cannizzaro reaction of aldehydes which are unaffected by alkali alone.

5-Chlorovanillyl alcohol was prepared and identified.

Reaction with alkali and 0.5 mole of silver oxide provides a simple laboratory method for the preparation of *o*- and *p*-hydroxy-substituted benzoic acids from their corresponding aldehydes.

APPLETON WIS.

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[FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

THE REACTION OF ETHYLENE OXIDE WITH ALKYLMAGNESIUM CHLORIDES

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Earlier work by Schlenk and Schlenk (1), Ribas and Tapia (2), and Huston and Agett (3) indicated that the reactions which take place when one mole of ethylene oxide is added to one mole of ethylmagnesium bromide may be represented by the following equations:

$$\text{(I)} \qquad 2C_2H_5MgBr \rightleftarrows (C_2H_5)_2Mg + MgBr_2$$

$$\text{(II)} \qquad MgBr_2 + 2(CH_2)_2O \rightarrow Br_2C_4H_8O_2Mg$$

Direct hydrolysis of the addition product, without heating, gave sixty to seventy per cent yield of ethylene bromohydrin and little or no *n*-butyl alcohol (3). The principal reaction may be represented according to the. equation:

$$\text{(III)} \qquad Br_2C_4H_8O_2Mg + 2H_2O \rightarrow 2BrCH_2CH_2OH + Mg(OH)_2$$

Good yields of *n*-butyl alcohol were obtained either by heating the reaction mixture:

$$\text{(IV)} \qquad (C_2H_5)_2\,Mg + Br_2C_4H_8O_2Mg \rightarrow (C_4H_9O)_2Mg + MgBr_2$$

or by adding a second mole of ethylene oxide:

$$\text{(V)} \qquad (C_2H_5)_2Mg + 2(CH_2)_2O \rightarrow (C_4H_9O)_2Mg$$

Hydrolysis of the addition product obtained by use of two moles of ethylene oxide gave a mixture of *n*-butyl alcohol and ethylene bromohydrin.

The purpose of the present investigation was to examine the behavior of alkylmagnesium chloride solutions and ethylene oxide under similar conditions.

Hydrolysis of the reaction mixture formed by adding ethylene oxide to ethylmagnesium chloride in a 1:1 molar ratio, without heating, gave a 54.6% yield of *n*-butyl alcohol and 22.0% of ethylene chlorohydrin based upon the titrated Grignard reagent (4). These results represent only the amounts actually recovered from the ether layer. They do not take into account the appreciable quantity of ethylene chlorohydrin destroyed during hydrolysis and that remaining in the water layer after extraction with ether.

A precipitate was formed by adding ether to the reaction mixture obtained from equal molecular quantities of ethylmagnesium chloride and ethylene oxide. This precipitate upon hydrolysis gave *n*-butyl alcohol. The chlorine content of nine precipitates varied between 27.03 and 36.34% and the magnesium content between 16.47 and 18.21%.

In some cases the ethylmagnesium chloride was prepared by use of ethylmagnesium bromide as a catalyst; in other cases no starter was used. The presence or absence of a catalyst seemed to make no difference either in the results of analysis or in the yields of alcohol and chlorohydrin.

Since butoxymagnesium chloride contains 26.7% chlorine and 18.3% magnesium, the values obtained indicate that the precipitate may have consisted largely of either butoxymagnesium chloride resulting from the reaction:

(VI) $$C_2H_5MgCl + (CH_2)_2O \rightarrow C_4H_9OMgCl$$

or $(C_4H_9O)_2\ Mg \cdot XMgCl_2$ formed by the reactions:

(VII) $$(C_2H_5)_2Mg + 2(CH_2)_2O \rightarrow (C_4H_9O)_2Mg$$

(VIII) $$(C_4H_9O)_2Mg + XMgCl_2 \rightarrow (C_4H_9O)_2Mg \cdot XMgCl_2$$

Hydrolysis of either intermediate would yield *n*-butyl alcohol.

However, when the molar ratio of ethylene oxide to ethylmagnesium chloride was 2:1, there was obtained an 80.3% yield of *n*-butyl alcohol and 69.4% yield of ethylene chlorohydrin. If the intermediate compound leading directly to the formation of a large amount of *n*-butyl alcohol were butoxymagnesium chloride, insufficient magnesium chloride would be left in solution to give this yield of ethylene chlorohydrin.

Even so, butoxymagnesium chloride may still be considered a possible intermediate, if it is assumed that as the solution becomes depleted of magnesium chloride, decomposition occurs according to the equation:

(IX) $$2C_4H_9OMgCl \rightarrow (C_4H_9O)_2Mg + MgCl_2$$

Thus it seems evident that the immediate precursor of the *n*-butyl alcohol is dibutoxymagnesium which could be formed by the reaction of ethylene oxide with either ethylmagnesium chloride or diethylmagnesium.

The reaction of the epoxide with diethylmagnesium appears more probable in view of the fact that ethylmagnesium chloride, according to Schlenk (5), is approximately eighty-five per cent dissociated into diethylmagnesium and magnesium chloride.

Evidence submitted by Noller and Castro (6) substantiates the theory that dibutoxymagnesium combines with varying amounts of magnesium chloride. They observed that the precipitate formed by the oxidation of *n*-butylmagnesium chloride removed magnesium chloride from solution. Noller and Castro suggested that if butoxymagnesium chloride is the product of oxidation, it should have the property of forming a complex with magnesium chloride, probably by virtue of the unshared electrons on the oxygen atom. Obviously dibutoxymagnesium should behave like butoxymagnesium chloride in this respect.

Further evidence for the precipitation of $(C_4H_9O)_2Mg \cdot XMgCl_2$ was provided by analysis of the precipitate formed by the use of one-half mole of ethylene oxide to one of ethylmagnesium chloride. In this case the chloride content was found to be 40.8% and the magnesium content was 19.6%. These are much higher values than the ones obtained when equimolecular quantities of the reactants were used. This is the result that should be expected under these conditions since more magnesium chloride would be available to precipitate with dibutoxymagnesium. Theoretical values for $(C_4H_9O)_2Mg \cdot 2MgCl_2$ are 39.3% chlorine and 20.2% magnesium.

There are two possible intermediates for ethylene chlorohydrin: chloroethoxymagnesium chloride formed by the reaction:

$$\text{(X)} \qquad MgCl_2 + (CH_2)_2O \rightarrow ClC_2H_4OMgCl$$

or dichlorodiethoxymagnesium formed by the reaction:

$$\text{(XI)} \qquad MgCl_2 + 2(CH_2)_2O \rightarrow (ClC_2H_4O)_2Mg$$

According to equation (X) the theoretical yield of ethylene chlorohydrin per mole of Grignard reagent is one-half mole. However, if the percentage yield is calculated on this basis, when ethylene oxide and ethylmagnesium chloride come into reaction in a 2:1 molar ratio, the amount of halohydrin actually obtained leads to far more than a hundred per cent. Hence, we feel justified in the assumption that the intermediate leading to ethylene chlorohydrin is dichlorodiethoxymagnesium.

TABLE I

PERCENTAGE YIELDS OF ALCOHOLS AND ETHYLENE CHLOROHYDRIN BASED UPON THE TITRATED GRIGNARD REAGENTS

R IN RMgCl	$RMgCl + C_2H_4O$ NOT HEATED		$RMgCl + C_2H_4O$ HEATED		$RMgCl + 2C_2H_4O$ NOT HEATED	
	Alcohol	Chlorohydrin	Alcohol	Chlorohydrin	Alcohol	Chlorohydrin
Ethyl	54.6	22.0	45.9	16.4	80.3	69.4
n-Propyl	39.5	31.5	49.9	32.0	66.4	54.0
Isopropyl	34.5	35.1	46.5	19.5	54.8	58.0
n-Butyl	39.0	25.5	45.8	36.8	69.6	60.1
s-Butyl	25.6	30.9	35.1	23.9	40.9	61.5
Isobutyl	23.6	34.6	29.8	25.0	35.2	60.4
t-Butyl	0.0	21.3	0.0	23.3	0.0	48.1

A survey was made of the reaction of ethylene oxide with the Grignard reagents of several alkyl chlorides. The yield of the alcohol and of ethylene chlorohydrin was determined in each case.

The Grignard reagents were prepared from the alkyl halide and pure magnesium turnings. All reactions and transfers were carried out in an atmosphere of nitrogen. Each Grignard reagent was treated in three different ways:

1. Treated with one mole of ethylene oxide and hydrolyzed without heating.
2. Treated with one mole of ethylene oxide and then refluxed with benzene before hydrolysis.
3. Treated with two moles of ethylene oxide and hydrolyzed without the addition of benzene or heating.

The results of the three methods of procedure are compared in Table I.

The table shows that three of the Grignard reagents reacted with ethylene oxide in a mole-per-mole ratio without heating to give the alcohol as the principal product. *s*-Butylmagnesium chloride and isobutylmagnesium chloride gave somewhat higher yields of halohydrin than of the alcohols. In agreement with results reported by Whitmore (7), *t*-butylmagnesium chloride, when treated with ethylene oxide, yielded only ethylene chlorohydrin.

The data also reveal that in respect to the two secondary Grignard reagents and isobutylmagnesium chloride, heating the reaction product before hydrolysis appears to enhance somewhat the yield of the alcohol at the expense of the halohydrin. In other cases the result of heating was to increase the yields of both the alcohol and of the ethylene chlorohydrin. The reaction product from ethymagnesium chloride and ethylene oxide could not be heated successfully because the mixture solidified upon attempting to distil off the ether prior to heating with benzene. This resulted in considerable decomposition of the intermediate product due to excessive heating near the side-walls of the flask.

In most cases addition of two moles of ethylene oxide to one mole of the Grignard reagent greatly increased the yield of both the alcohol and the ethylene chlorohydrin.

When the boiling points of the alcohol and halohydrin were too close together to allow a good separation by distillation, the two compounds were collected together. The chlorohydrin was determined by hydrolysis with sodium hydroxide and titration of the chloride ion by the Volhard method. The alcohol was determined by difference.

Attempts to prepare dichlorodiethoxymagnesium in the pure state by treating a stirred suspension of dry magnesium chloride with ethylene oxide were not successful. This was accomplished by the treatment of diethylmagnesium in ether solution with the molecular equivalent of ethylene chlorohydrin. The solid compound dissolved readily in cold ethylmagnesium chloride. Hydrolysis of the precipitate, either directly or after dissolving in Grignard reagent (C_2H_5MgCl), gave ethylene chlorohydrin.

EXPERIMENTAL

Preparation of ethylmagnesium chloride Two and one-quarter moles (54.7 g.) of magnesium turnings was placed in a dry two-liter, three-necked, round-bottomed flask. The flask was fitted with a mercury-sealed stirrer which was equipped with an inlet tube for nitrogen, a "dry-ice" condenser, and an inlet tube for ethyl chloride. The ethyl chloride tube extended nearly to the bottom of the flask. After flushing out the system with dry nitrogen and ethyl chloride, one liter of anhydrous ether was added to the flask and the reaction catalyzed by the addition of a small amount of ethylmagnesium bromide. "Dry-ice" was then placed in the condenser. Ethyl chloride was bubbled through concentrated sulfuric acid and added at such a rate as to maintain a moderate rate of reaction. After most of the magnesium had reacted, addition of the ethyl chloride was discontinued and stirring maintained until the reaction mixture reached room temperature. This latter stage of the reaction was carried out in a very slow stream of nitrogen. The flask was sealed off from air and allowed to stand overnight.

Preparation of other Grignard reagents. Two and one-quarter moles (54.7 g.) of magnesium turnings was placed in a two-liter flask fitted with a mercury-sealed stirrer which was equipped with an inlet tube for nitrogen, a reflux condenser, and a dropping-funnel. After flushing out the system with dry nitrogen, four or five grams of the alkyl halide mixed with one hundred ml. of anhydrous ether was added to the flask. The reaction was started by the addition of a small amount of ethylmagnesium bromide and an additional hundred ml.

of ether. The balance of the alkyl halide to make a total of two moles was mixed with eight hundred ml. of ether and added at such a rate as to maintain moderate refluxing. After addition was complete, a slow stream of nitrogen was introduced and stirring continued for two hours. The product was allowed to stand overnight. The preparation of *t*-butylmagnesium chloride was carried out very slowly.

Reaction of ethylene oxide and Grignard reagent in a 1:1 molar ratio. A standard acid-base titration (4) was used to determine the concentration of the Grignard reagent. The total volume of the solution was measured, and it was transferred (in an atmosphere of nitrogen) to another three-necked, round-bottomed flask. This flask was also fitted with a mechanical stirrer, reflux condenser, and a dropping-funnel equipped with an outer metal jacket to permit the use of "Dry-ice" as a cooling agent. The Grignard reagent was cooled in an ice-salt bath. One hundred ml. of anhydrous ether was placed in the dropping-funnel and surrounded with "Dry-ice." The calculated amount of ethylene oxide which previously had been dried over soda-lime was weighed out and placed in the dropping-funnel. The ethylene oxide-ether mixture was cautiously added to the Grignard reagent. As soon as addition was complete, the ice-salt bath was removed and the mixture was allowed to stir for an hour. The product was hydrolyzed by pouring it on chipped ice. After hydrolysis the ether layer was decanted. The pasty magnesium hydroxide was extracted three times with small portions of ether, neutralized with dilute hydrochloric acid (iced), and again extracted three times with ether. The ether extracts were combined, dried over sodium sulfate and fractionated through a twelve-inch, Fenske-type column packed with $\frac{3}{32}$ inch glass helices.

Reaction of ethylene oxide and Grignard reagent in a 1:1 molar ratio followed by heating. After adding the ethylene oxide to the Grignard reagent as described above, the condenser was set for distillation. The reaction-flask was placed in a Glas-Col heating mantle and about seven hundred ml. of ether removed. The temperature of the reaction mixture was not allowed to exceed 45°. Five hundred ml. of anhydrous benzene was added and gentle refluxing continued for six hours. The product was hydrolyzed, extracted, dried, and fractionated as described in the previous experiment.

Reaction of ethylene oxide and Grignard reagent in a 2:1 molar ratio. The calculated amount of ethylene oxide was mixed with one hundred ml. of anhydrous ether and added to the Grignard reagent according to the procedure described above. Since the ethylene oxide tended to polymerize, it was usually not possible to stir the mixture for an hour after addition was complete. The product was hydrolyzed immediately, extracted, dried, and fractionated as previously described.

Analysis of the intermediate compound from the reaction of ethylene oxide and Grignard reagent in a 1:1 molar ratio. The preparation of the Grignard reagent (C_2H_5MgCl) and addition of ethylene oxide was accomplished according to the previously described procedure. Part of the reaction mixture was diluted with ether and centrifuged for ten minutes at 1800 r.p m. The precipitate was washed with ether, transferred quickly to a weighing-bottle which was placed in a desiccator and evacuated with a water-pump for three hours and with an oil-pump at about 2 mm. for twelve hours. Total chlorine was determined by sodium peroxide fusion in a Parr bomb and subsequent titration by the Volhard method. Magnesium was determined as MgO after heating to constant weight with a Meker burner.

Determination of the alcohol and ethylene chlorohydrin. The product was distilled and the alcohol and halohydrin fractions collected together. After determining the total weight of the distillate, five hundred ml. of 0.3 molar sodium hydroxide was added and the mixture refluxed with stirring for a half hour. The contents of the flask was cooled, placed in a separatory funnel and the water-layer drawn off into a liter volumetric flask. The solution was made up to volume and five-ml. samples taken for analysis. Chlorine was determined by means of the Volhard method. The amount of ethylene chlorohydrin was calculated from the results of the chloride analysis and the weight of the alcohol obtained by difference.

Preparation of dichlorodiethoxymagnesium. One mole of diethylmagnesium in solution was added, dropwise, to a stirred solution containing one mole of ethylene chlorohydrin in ether. The reaction mixture was centrifuged and the precipitate washed with anhydrous ether.

Calc'd for $C_4H_8Cl_2MgO_2$: Cl, 38.68; Mg, 13.27.

Found: Cl, 37.92; Mg, 13.87.

The precipitate was suspended in anhydrous ether and Grignard reagent (C_2H_5MgCl) was added drop by drop until solution was complete. Hydrolysis of dichlorodiethoxymagnesium, either in ether suspension or in solution, gave ethylene chlorohydrin.

SUMMARY

1. The main reaction between one mole of ethylene oxide and one mole of Grignard reagent formed by the treatment of alkyl chlorides with magnesium is between the epoxide and either dialkylmagnesium or alkylmagnesium chloride.

2. The intermediate in the formation of *n*-butyl alcohol from diethylmagnesium is dibutoxymagnesium. From ethylmagnesium chloride it is butoxymagnesium chloride which by rearrangement gives dibutoxymagnesium and magnesium chloride. The high yield of both alcohol and chlorohydrin when excess of ethylene oxide is used indicates, in the main, dibutoxymagnesium.

3. Analytical results indicate that the composition of the precipitate formed when the reaction mixture of one mole of ethyl Grignard reagent and one mole of ethylene oxide is diluted with ether approaches $(C_4H_9O)_2Mg \cdot MgCl_2$. When the ratio of Grignard reagent to ethylene oxide is 2:1 it approaches the composition of $(C_4H_9O)_2Mg \cdot 2MgCl_2$.

4. Evidence submitted indicates that the precursor of the ethylene chlorohydrin is dichlorodiethoxymagnesium.

5. Results obtained by heating the reaction mixture from equal molecular quantities of alkylmagnesium chloride and ethylene oxide do not indicate a high degree of reactivity between dichlorodiethoxymagnesium and dialkylmagnesium.

6. Addition of two moles of ethylene oxide to one of alkylmagnesium chloride greatly increased the yields of both the alcohol and ethylene chlorohydrin.

East Lansing, Mich.

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[Contribution from the Cobb Chemical Laboratory, University of Virginia]

ANTIMALARIALS.[1] AMIDES RELATED TO PHENYLPANTOTHENONE

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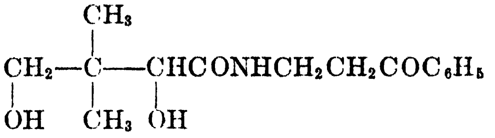
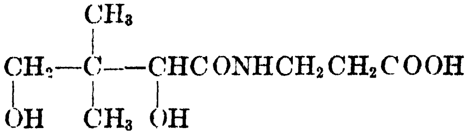
The discovery of the activity against avian malaria of (+)-phenylpantothenone (I) (1),[3] which is configurationally related to the natural pantothenic acid (II), warranted a further investigation of compounds of this type. This work was undertaken at the request of the Panel on Synthesis of Antimalarial Drugs,[1] and is concerned with the preparation of some amides which are structurally related to phenylpantothenone. Variations were designed to show the effect on antimalarial activity of (a) inverting the stereochemical configuration; (b) substituting less complex groups for the pantoyl portion of the molecule; (c) modifying the propiophenone portion of the pantothenone molecule by removing one methylene group; (d) by removing the carbonyl group; (e) by various substitutions of possible activating groups in the phenyl nucleus; and (f) by reducing the carbonyl group to the alcohol.



$$HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2COC_6H_5$$

I



$$HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2COOH$$

II

The results to date, discussed in the above order, are as follows:

(a) Using a modification of the procedure of Woolley and Collyer (1b), both (−)-and (+)-pantolactones were condensed with β-aminopropiophenone in yields of 40–50%. The resulting (+)- and the new (−)-pantothenones were oils which could not be distilled even at very low pressures. Woolley and Collyer (1b) reported that (+)-phenylpantothenone was obtained as a crystalline solid (m.p. 126°) but we were unable to confirm this finding. The analytical data on these oils checked closely with the theoretical values, and the specific rotation figures for the two products were opposite in sign and of the same numerical magnitude (−35.4 and +37.1). Furthermore, the specific rotation of the (+)-tolylpantothenone (XII), which was obtained in an analytically pure, crystalline form (m.p. 88–90°), was not markedly higher (+41.1).

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[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

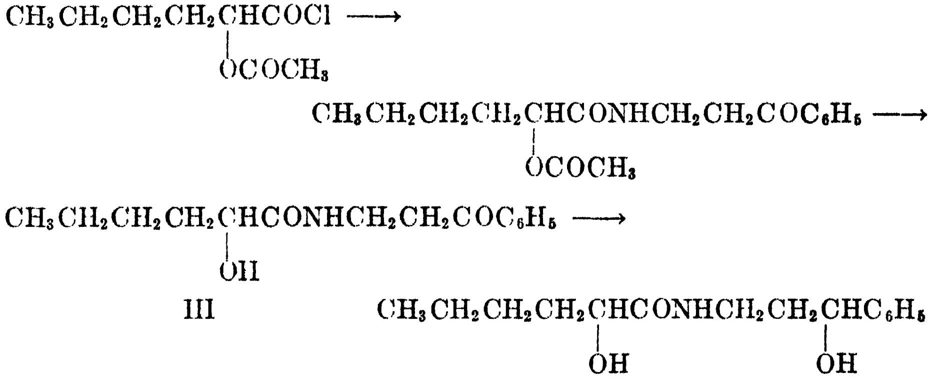
The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which the Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

[2] Present address: (a) Smith, Kline, and French Laboratories, Philadelphia, Pa.; (b) Heyden Chemical Corp., Fords, N. J.; (c) Middlebury College, Middlebury, Vermont.

[3] Dr. K. C Blanchard was instrumental in having this compound tested.

The (−)-phenylpantothenone (of configuration opposite to that of pantothenic acid) was inactive against avian malaria, showing the activity to be specific with respect to the natural pantothenic configuration.

(b) No difficulty was encountered in condensing caproyl chloride with β-aminopropiophenone. α-Acetoxycaproyl chloride was also condensed with the amino ketone. Preferential hydrolysis of the latter gave the hydroxy amide (III) and aluminum isopropoxide reduction yielded the dihydroxy amide (IV).



$$CH_3CH_2CH_2CH_2\underset{OCOCH_3}{\underset{|}{C}}HCOCl \longrightarrow$$

$$CH_3CH_2CH_2CH_2\underset{OCOCH_3}{\underset{|}{C}}HCONHCH_2CH_2COC_6H_5 \longrightarrow$$

$$CH_3CH_2CH_2CH_2\underset{OH}{\underset{|}{C}}HCONHCH_2CH_2COC_6H_5 \longrightarrow$$

III

$$CH_3CH_2CH_2CH_2\underset{OH}{\underset{|}{C}}HCONHCH_2CH_2\underset{OH}{\underset{|}{C}}HC_6H_5$$

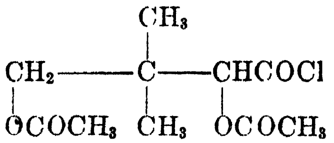
IV

Repeated attempts to react γ-butyrolactone with β-aminopropiophenone were without success.

The lack of antimalarial activity among these compounds confirmed expectation based on the specificity of the natural pantothenic configuration.

(c) Efforts to condense α-aminoacetophenone with (−)-pantolactone employing essentially the procedure used in preparing phenylpantothenone, were unsuccessful. This failure was probably due to the sensitivity of aminoacetophenone (2) in the form of the free base.

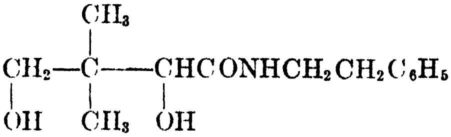
It was thought that perhaps the diacetyl derivative of pantoyl chloride (3) (V) could be condensed with α-aminoacetophenone. Removal of the acetyl



$$\underset{OCOCH_3}{\underset{|}{CH_2}}—\overset{CH_3}{\underset{CH_3}{\underset{|}{\overset{|}{C}}}}—\underset{OCOCH_3}{\underset{|}{C}}HCOCl$$

groups by preferential hydrolysis should then be possible and should give the desired amide. Judging from the ease with which caproyl chloride was condensed with aminoacetophenone, and from the successful selective hydrolysis of the acetyl derivative of N-(β-benzoylethyl)-α-hydroxycaproamide (see III), this method should be a feasible one; however, this project was not completed.

(d) β-Phenylethylamine was readily condensed with (+)-, (−)-, and (*dl*)-pantolactones to give the amides (VI).

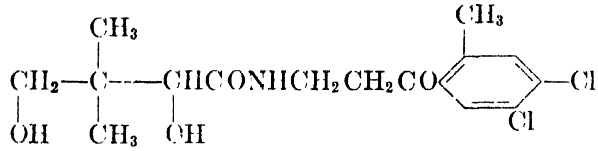


$$\begin{array}{lll} & \mathrm{CH_3} & \\ & | & \\ \mathrm{CH_2} & \!\!—\mathrm{C}—\!\! & \mathrm{CHCONHCH_2CH_2C_6H_5} \\ | & | & | \\ \mathrm{OH} & \mathrm{CH_3} & \mathrm{OH} \end{array}$$

VI

The *dl* amide (m.p. 92–93°) proved to be inactive against avian malaria [*cf.* (a)].

(e) In an effort to increase the antimalarial activity of (+)-phenylpantothenone by means of nuclear activating groups, [*cf.* (f)], 4-methyl-, 4-chloro-, and 2-methyl-4,5-dichloro-β-aminopropiophenones were prepared and condensed with (−)-pantolactone. All of the products thus obtained (*cf.* VII)



VII

were active against avian malaria, but only the *p*-chloro compound showed significant increase in activity as compared with (+)-phenylpantothenone itself.

In several of the condensations of the pantolactone with the β-aminopropiophenones, crystalline by-products were formed from the aminopropiophenones, evidently by autocondensation, since the aminopropiophenones alone when subjected to the condensation conditions gave the same materials. Three of these autocondensation products were purified. Analyses indicated that they were tertiary amines of the general formula $(RCOCH_2CH_2)_3N$. Substantiation of these structures is offered by the work of Blicke and Burckhalter (4) on methyl-(β-benzoylethyl)amine, which in the presence of alkali loses methylamine and forms the vinyl ketone. Reaction of a second molecule of methyl-(β-benzoylethyl)amine with the vinyl ketone then gives methyl-di-(β-benzoylethyl) amine.

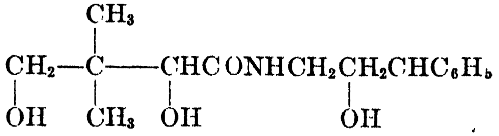
In a similar way the autocondensation of aminopropiophenone can be represented as follows:

$$\underset{\text{VIII}}{C_6H_5COCH_2CH_2NH_2} \rightarrow \underset{\text{IX}}{C_6H_5COCH{=}CH_2} \xrightarrow{+\ \text{VIII}}$$

$$(C_6H_5COCH_2CH_2)_2NH \xrightarrow{+\ \text{IX}} \underset{\text{X}}{(C_6H_5COCH_2CH_2)_3N}$$

The tri-(β-benzoylethyl)amine (X) was tested and found to be inactive against avian malaria.

(f) Several attempts were made to prepare phenylpantothenol (XI) in order to determine the effect of converting the ketone into a secondary alcohol. In



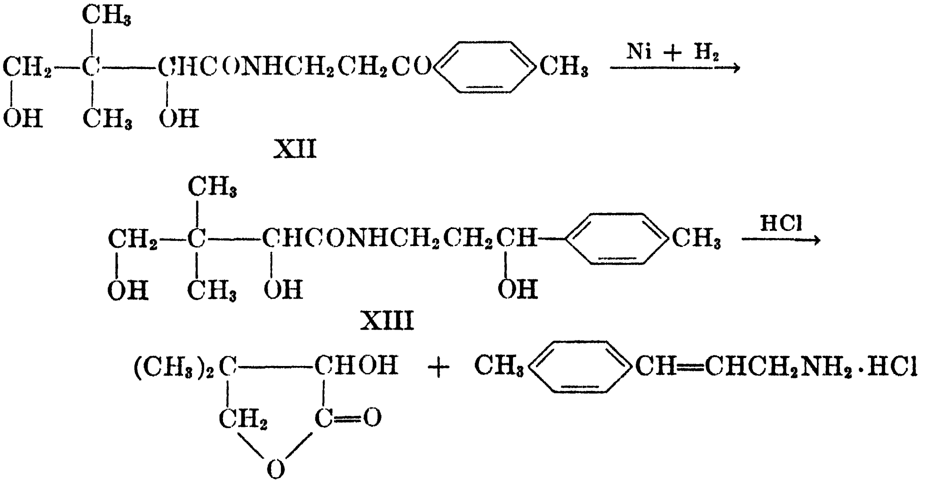
$$\begin{array}{l} \qquad\ \ CH_3 \\ CH_2{-}\overset{|}{\underset{|}{C}}{-}\underset{|}{C}HCONHCH_2CH_2\underset{|}{C}HC_6H_5 \\ \underset{|}{}OH \quad CH_3\ \ OH \qquad\quad\ OH \end{array}$$

XI

an effort to synthesize this compound directly we planned to condense γ-hydroxy-γ-phenylpropylamine with the lactone. The γ-hydroxy-γ-phenylpropylamine (5) was readily prepared by catalytic reduction of β-aminopropiophenone. However, repeated attempts to condense this amino alcohol with the lactone failed.

Phenylpantothenone, itself, with both Raney nickel and platinum catalysts showed a consistently anomalous behavior in attempted reductions (see experimental section). The results with aluminum isopropoxide were equally unsatisfactory.

Tolylpantothenone (XII) was used in subsequent reduction experiments because it was obtained as a pure crystalline solid and was as active as the phenyl analog. Using Raney nickel catalyst and alcohol as solvent, the required volume of hydrogen was readily absorbed. The colorless viscous oil obtained was shown to be the desired tolylpantothenol (XIII) as follows: A Zerewitinoff deter-



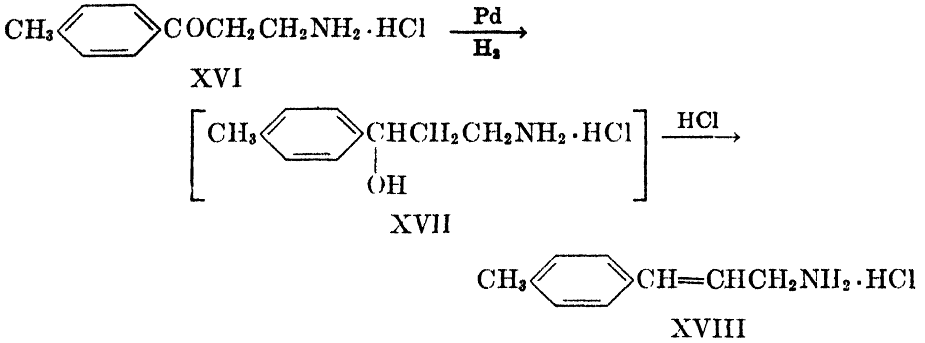
XII

XIII

XIV XV

mination showed the expected four active hydrogens, whereas the unreduced tolylpantothenone showed only three. Hydrolysis of the tolylpantothenol according to the method of Woolley and Collyer (1b) gave the (−)-pantolactone (XIV) and a hydrochloride which melted at 239–240°, and which from the analysis appeared to be γ-(4-methylphenyl)allylamine (XV). In contrast with this result, hydrolysis of the unreduced compound gave β-amino-4-methylpropiophenone hydrochloride (m.p. 183°) and XIV.

In order to prove that the hydrochloride (m.p. 239–240°) consisted of some degradation product of the alcohol, namely γ-hydroxy-γ-(4-methylphenyl)propylamine (XVII), a sample of β-amino-4-methylpropiophenone hydrochloride itself (XVI) was catalytically reduced, using the method of Davies and Powell (5). The resulting alcohol (XVII) was not isolated, but was subjected to the same hydrolytic conditions used for preparing the pantothenol (XIII). In this way a hydrochloride (XVIII) was obtained (m.p. 240–241°) which proved to be identical with the hydrochloride obtained upon hydrolysis of the pantothenol (XIII).



The structure of this hydrochloride, namely, γ-(4-methylphenyl)allylamine (XVIII), was substantiated by analogy to the behavior of the phenyl compound. γ-Hydroxy-γ-phenylpropylamine under the same hydrolytic conditions employed with tolylpantothenol, gave the known γ-phenylallylamine hydrochloride (6) (m.p. 235°; picrate, m.p. 179–180°).

Tolylpantothenol (XIII) proved to be only very slightly active against avian malaria.

Samples of all the new compounds tested against malaria were also submitted to Dr. D.W. Woolley of The Rockefeller Institute for Medical Research and were tested for bacteriostatic activity on *Lactobacillus casei;* the results are shown in Table I, in which the activities are expressed as fractions of the activity of (+)-phenylpantothenone.

The three compounds containing the pantoyl moiety, of configurations corresponding to that of pantothenic acid, and only these, were found to possess antimalarial activity and action also against *Lactobacillus casei;* however, the relative bacteriostatic activities of these compounds did not parallel the relative antimalarial activities.

Acknowledgment. A great deal of assistance in the above described work was rendered by the following: Gilbert Ashburn, Philip S. Bailey, Marion T. Clark, Norman H. Leake, Russell J. Rowlett, Jr., Jason M. Salsbury and Newton H. Shearer, Jr. Most of the microanalyses were performed by Miss Joyce Blume and Curtis J. Floyd.

TABLE I

BACTERIOSTATIC ACTIVITY

COMPOUND	ACTIVITY
(−)-Phenylpantothenone	less than 0.03
(+)-*p*-Chlorophenylpantothenone	2.7
(+)-*p*-Tolylpantothenone	7
(+)-*p*-Tolylpantothenol	0.7
N-(β-Benzoylethyl)-α-hydroxycaproamide	less than 0.05
N-(β-Benzoylethyl)caproamide	less than 0.05
dl-N-pantoyl-β-phenylethylamide	less than 0.05
Methyldi(benzoylethyl)-amine[4]	0.07

EXPERIMENTAL[5]

β-Chloropropiophenone (m.p. 49–50°) was prepared in 80–90% yield using the procedure of Allen and Barker (7).

β-Phthalimidopropiophenone. The method of Hale and Britton (8) was modified for large scale preparation. An intimate mixture of 53 g. of the chloro ketone and 59.5 g. of potassium phthalimide (9) was heated at 130° in an oil thermostat for one hour with efficient stirring. The melt was poured from the flask while still hot. After solidification it was ground to a powder, triturated with water, and crystallized from ethanol; m.p. 129–130°; yield 81%. The crude product, however, gave satisfactory results in the next step.

β-Aminopropiophenone hydrochloride (*SN-14,253*). The procedure used was essentially that of Davies and Powell (5); yields of 80–85% were realized.

(−)-Phenylpantothenone (*SN-13,767*). This compound was prepared by the following method, which is a modification of that used by Woolley and Collyer (1) to obtain the compound corresponding to the natural pantothenic acid (of opposite stereochemical configuration). Twenty grams of β-aminopropiophenone hydrochloride was dissolved in 120 ml. of cold 5% sodium hydroxide. The free base was extracted from this with six 150-ml. portions of ether. The ether solution was shaken with 50 ml. of saturated sodium chloride solution and dried for one hour over sodium sulfate. The ether and traces of water were removed by evaporation under reduced pressure (0–25°) employing first a water and than a "hyvac" pump. The pale yellow oil (14.2 g.) which remained was heated with 12.4 g. of (+)-pantolactone at 82° for three hours. The resulting red oil was dissolved in 100 ml. of methanol and sufficient hydrochloric acid (1.06 *N*) was added to bring the *p*H to 3. This solution was diluted with water until slightly cloudy, cooled to 0°, and filtered to remove a small quantity of white by-product (see below). The filtrate was extracted with five 200-ml. portions of ether. The combined ether solution was shaken with two 35-ml. portions of 1 *N* sodium hydroxide solution and then with 50 ml. of saturated sodium chloride solution which contained sufficient hydrochloric acid to give this wash solution a *p*H of 6 after separation. After drying for one hour over sodium sulfate the ether was removed by evaporation under

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[4] *Cf.* reference (4).

[5] Melting points reported herein are corrected.

reduced pressure. Any remaining volatile solvent was removed under reduced pressure over a prolonged period (20 hours) at room temperature with frequent agitation. Repeated attempts to crystallize this extremely viscous oil were unsuccessful. It weighed 10 g. (40%); $[\alpha]_D^{28}$ −33.4° ($c = 2.73$) in absolute ethanol.

Anal. Calc'd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.02.

Found (different samples): C, 64.22, 64.79, 63.41; H, 7.18, 7.07, 7.62; N, 4.52, 4.53, 4.46.

Tri-(β-benzoylethyl)amine (*SN-14,219*) from the preceding condensation melted at 144–145° after several crystallizations from ethanol.

Anal. Calc'd for $C_{27}H_{27}NO_3$: C, 78.42, H, 6.58; N, 3.36.

Found: C, 77.44; H, 6.47; N, 3.36, 3.25, 3.31.

(+)-Phenylpantothenone (*SN-12,610*). This compound was first prepared by Woolley and Collyer (1) and was prepared by us from (−)-pantolactone and β-aminopropiophenone using the modified procedure described for the (−)-phenylpantothenone. The by-product (m.p. 144–145°) that was obtained in the preceding condensation was also obtained here. Attempts in this laboratory to crystallize this compound were unsuccessful. It was obtained in yields of 40–50%; $[\alpha]_D^{20}$ +37.1° ($c = 0.998$) in absolute ethanol.

Anal. Calc'd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58.

Found (different samples): C, 64.79, 65.29, 65.49; H, 7.11, 7.45, 7.49.

N-(2-Benzoylethyl)caproamide (*SN-13,771*). To a solution of 15 g. of β-aminopropiophenone hydrochloride in 150 ml. of cold water was added with stirring 15 g. of *n*-caproyl chloride and then 65 ml. of 15% sodium hydroxide solution. After stirring for thirty minutes the amorphous white solid was filtered and recrystallized from benzene-ligroin; 15 g. (75%); m.p. 63–65°. Two additional recrystallizations raised the melting point to 65–66°.

Anal. Calc'd for $C_{15}H_{21}NO$: C, 72.84; H, 8.56; N, 5.66.

Found: C, 73.46; H, 8.89; N, 5.78.

dl-α-Hydroxycaproic acid. A preparative method for this compound has been described in the literature (10). The following method, however, eliminates the necessity of isolating the product through its copper salt.

A solution of 170 g. of α-bromocaproic acid (11) in 2 l of 10% sodium carbonate was refluxed for six hours. The resulting straw colored solution was cooled in an ice-bath and carefully neutralized with concentrated sulfuric acid. Continuous extraction (24 hours) with ether and removal of the ether by evaporation under reduced pressure gave 115 g. of a mobile oil. Cooling in an ice-chest for twelve hours gave 29 g. of white plates. Prolonged cooling gave an additional 15 g. of product; total yield 44 g. (42%); m.p. 59-61°.

dl-N-(2-Benzoyethyl)-α-hydroxycaproamide (*SN-13,773*). A mixture of 20 g. of α-hydroxycaproic acid and 35 g. of acetyl chloride was refluxed for five minutes. The excess acetyl chloride was removed by distillation and the residual straw colored syrup was refluxed for three hours with 64 g. of thionyl chloride. The excess thionyl chloride was removed by distillation under reduced pressure. The residual crude acid chloride was added at once with stirring to a cold (0°) solution of 24.6 g of β-aminopropiophenone hydrochloride in 200 ml. of water. After stirring for fifteen seconds a cold solution of sodium hydroxide (11.9 g. in 80 ml. of water) was added. A viscous oil soon separated and quickly solidified. After stirring for ten minutes the solid was filtered and washed well with water; yield 31.5 g. (66%); m.p. 58–64°. Eighteen grams of this crude acetyl derivative was hydrolyzed by dissolving in 170 ml. of ethanol containing 2.5 g. of sodium hydroxide and allowing the resulting solution to stand at room temperature for five hours. Dilution with 50 ml. of water and cooling gave 13 g. (82%) of a white crystalline precipitate; m.p. 118–119°. Recrystallization from benzene gave 11 g. melting at 118–119°.

Anal. Calc'd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32.

Found: C, 68.48; H, 8.34; N, 4.90.

The *semicarbazone* after crystallization from an ethanol-water solution melted at 159–160°.

Anal. Calc'd for $C_{16}H_{24}N_4O_3$: N, 17.49. Found: N, 17.35.

dl-N-1-[(3-Hydroxy-3-phenyl)propyl]-α-hydroxycaproamide. A solution of 6.5 g. of N-(β-benzoylethyl)-α-hydroxycaproamide and 20 g. of aluminum isopropoxide in 50 ml. of dry toluene was heated at reflux temperature for nineteen hours. The straw colored solution was cooled in an ice-bath and extracted with an excess of conc'd hydrochloric acid. The aqueous layer was separated and extracted with a small volume of toluene. The combined toluene solution was washed with water and dried over sodium sulfate. Sufficient ligroin was added to cause a slight cloudiness. Cooling overnight in an ice-chest gave 5 g. of a crude product melting at 65–80°. Three recrystallizations from ethanol-water gave a white crystalline product; m.p. 98–99°.

Anal. Calc'd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28.

Found: C, 67.81; H, 8.76; N, 5.06.

Attempts to prepare N-(β-benzoylethyl)-γ-hydroxybutyramide by condensing γ-butyrolactone (12) and β-aminopropiophenone, failed, using both the procedure of Woolley and Collyer and the modified procedure developed here. Consistently high yields of tri-(β-benzoylethyl)amine (m.p. 144–145°) were obtained. The oil which remained after the removal of this by-product could not be crystallized, and analytical data indicated that it was not the desired product.

Attempted preparation of (+)-phenylpantothenol. (a) γ-Phenyl-γ-hydroxypropylamine was prepared from β-aminopropiophenone hydrochloride by the method of Davies and Powell (5). On long heating (at 75° and 95°) with (−)-pantolactone the amino alcohol failed to condense, and none of the desired product could be obtained. In an earlier attempt to prepare γ-phenyl-γ-hydroxypropylamine, β-phthalimidopropiophenone was reduced to the corresponding alcohol with aluminum isopropoxide but all attempts to hydrolyze this compound to the amino alcohol were unsuccessful.

(b) In an attempt to reduce (+)-phenylpantothenone at room temperature and atmospheric pressure using Raney nickel catalyst and ethanol as solvent, the required volume of hydrogen was absorbed in a period of five hours. Using platinum catalyst the required volume of hydrogen was absorbed in four hours. The oily products, however, did not exhibit the expected properties. Zerewitinoff determinations showed that phenylpantothenone had three active hydrogens. Phenylpantothenol, then, should show four active hydrogens. The products in each case, however, possessed only three active hydrogens, indicating that no reduction had occurred. Furthermore, both of the oily products on hydrolysis with hydrochloric acid according to the method of Woolley and Collyer (1) gave only the (−)-lactone and β-aminopropiophenone hydrochloride, the products obtained when (+)-phenylpantothenone is hydrolyzed.

(c) (+)-Phenylpantothenone, when refluxed with an excess of aluminum isopropoxide in isopropanol for three hours, also gave a product which showed only three active hydrogens, and which gave only β-aminopropiophenone hydrochloride and the (−)-lactone on hydrolysis.

β-Phthalimidoethylbenzyl alcohol. Twenty-four grams of β-phthalimidopropiophenone was added to 200 cc. of dry isopropanol and 100 cc. of aluminum isopropoxide. Reduction by the Pondorff method was carried out for 2½ hours, after which the excess isopropanol was evaporated under reduced pressure. The resulting material was carefully hydrolyzed by adding 200 cc. of water and slowly dropping in dilute hydrochloric acid until *p*H 5 was reached. A thick brown oil resulted which was extracted into ether and dried over sodium sulfate. After evaporation of the ether an oil was left which crystallized upon slowly cooling a hot concentrated ether solution; 12.1 g. (50%); m.p. 75–76°; white needles.

Anal. Calc'd for $C_{17}H_{15}NO_3$: N, 4.98. Found: N, 4.81.

γ-Phenylallylamine hydrochloride. Both Posner (6a) and Emde (6b) have prepared this compound from cinnamyl chloride and ammonia. Posner reports the melting point 210° and Emde gives the melting point as 236°. The picrate according to Posner melts at 173°. The hydrochloride was prepared in this laboratory in approximately 60% yield by subjecting γ-hydroxy-γ-phenylpropylamine hydrochloride to the same conditions which

Woolley and Collyer (1b) used to hydrolyze (+)-phenylpantothenone. It melted at 235°. The picrate melted at 179–180°.

β-Chloro-p-methylpropiophenone, made by the method of Kenner and Statham (13) and crystallized from hexane, melted at 77–80°; yield 56%.

p-Methyl-β-phthalimidopropiophenone. This compound was obtained in 87% yield using the same procedure employed in preparing β-phthalimidopropiophenone itself. The crude product was used without further purification. An analytical sample, prepared by crystallization from ethanol, melted at 132–135°.

Anal. Calc'd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15.
Found: C, 73.80; H, 5.32.

β-Amino-p-methylpropiophenone hydrochloride. The method which Davies and Powell (5) used in preparing β-aminopropiophenone hydrochloride was modified slightly in preparing the compound. The period of reflux was increased to twenty hours and additional hydrochloric acid was introduced during the course of the hydrolysis. The tolyl compound was less soluble in water than the phenyl analog and as a consequence a larger volume of water was required in separating it from the phthalic acid. The product (rectangular plates) was crystallized from ethanol-acetone in 71% yield; m.p. 182–186°.

Anal. Calc'd for $C_{10}H_{13}NO \cdot HCl$: C, 60.15; H, 7.07.
Found: C, 60.23; H, 7.29.

Tri-[(p-methylbenzoyl)ethyl]amine by autocondensation of β-amino-p-methylpropiophenone. Five grams of the amino ketone (free base) was heated at 70–80° for sixteen hours. When cold, the thick waxy oil was shaken with a small volume of ether. The small amount of white solid which separated was removed by filtration; m.p. 126–128°. Recrystallization from ethanol did not raise the melting point.

Anal. Calc'd for $C_{30}H_{33}NO_3$: C, 79.09; H, 7.30.
Found: C, 79.18; H, 7.36.

(+)-p-Tolylpantothenone (SN-14,688). The procedure used to prepare (−)-phenylpantothenone was modified slightly. The (−)-lactone and the free base were heated at 70–80° for sixteen hours. After the same purification procedure, the extremely viscous product was dissolved in a very small volume of benzene, and the solution stirred at 8° for fifty hours. Crystallization of the tolylpantothenone produced an almost solid mass. After dilution with ether the product was separated by filtration. Two recrystallizations from benzene gave a 36% yield; m.p. 88–90°; $[\alpha]_D^{22}$ +41.1° ($c = 2.190$) in absolute ethanol.

Anal. Calc'd for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90.
Found: C, 65.24; H, 7.96.

Hydrolysis of (+)-tolylpantothenone by the procedure of Woolley and Collyer (1) for hydrolyzing (+)-phenylpantothenone gave two products which were isolated and identified by mixture melting points with authentic samples; namely, β-amino-*p*-methylpropiophenone hydrochloride (m.p. 182–186°) and (−)-pantolactone (m.p. 88–91°).

(+)-p-Tolylpantothenol (SN-15,032). A solution of 15 g. of (+)-tolylpantothenone in 400 ml. of ethanol, containing 10 g. of Raney nickel, was hydrogenated at room temperature and atmospheric pressure. After fourteen hours the required volume of hydrogen was absorbed. Removal of the catalyst, and of the solvent by evaporation under reduced pressure at 45°, gave a viscous oil. This product, supposedly a mixture of epimers, was purified using the same procedure as was employed in purifiying (−)-phenylpantothenone. The clear oil thus obtained weighed 4 g. (27%); $[\alpha]_D^{19}$ +32.6° ($c = 1.133$) in absolute ethanol. A Zerewitinoff determination showed four active hydrogens (the unreduced compound showed only three).

Anal Calc'd for $C_{16}H_{25}NO_4$: C, 65.10; H, 8.52; N, 4.75; active hydrogens, 4.
Found: C, 64,18; H, 8.47; N, 4.68; active hydrogens, 4.12.

γ-(p-Tolyl)allylamine hydrochloride. Hydrolysis of (+)-*p*-tolylpantothenol by the procedure of Woollev and Collyer gave two products. One was shown to be (−)-pantolactone by a mixture melting point with an authentic sample. The other product, a hydrochloride, melted at 236–239° after crystallization from absolute ethanol.

Anal. Calc'd for $C_{10}H_{13}N \cdot HCl$: C, 65.50; H, 7.68; N, 7.63; Cl^-, 19.30.
Found: C, 65.10; H, 7.52; N, 7.30; Cl^-, 20.48.

In order to obtain additional evidence for the structure, 1 g. of β-amino-*p*-methylpropiophenone hydrochloride was catalytically reduced to the alcohol according to the procedure of Davies and Powell (5) for preparing γ-phenyl-γ-hydroxypropylamine. The alcohol was not isolated but it was subjected to the same conditions used in the hydrolysis of the (+)-*p*-tolylpantothenol. This procedure gave a white hydrochloride which melted at 240–241° after two recrystallizations from absolute ethanol. A mixture melting point with the hydrolysis product above (m.p. 236–239°) showed no depression.

β,p-Dichloropropiophenone. Allen, Cressman, and Bell (14), employing the method of Hale and Britton (8) as modified by Allen and Barker (7) for the preparation of *p*-phenyl-β-chloropropiophenone, prepared this compound in a 38% yield. A much improved yield was realized here by refluxing the Friedel-Crafts reaction mixture for three hours and then allowing it to stand overnight at room temperature. After hydrolysis and filtration the carbon disulfide phase was separated, shaken with dilute potassium carbonate solution, and with water. The carbon disulfide was removed by distillation under reduced pressure and the residual oil was dissolved in the minimum volume of hot ethanol. Treatment with decolorizing carbon followed by cooling gave a 63% yield of white crystalline product; m.p. 49–50° (A., C., and B., 48°).

p-Chloro-β-phthalimidopropiophenone. The same procedure was used here as was employed in preparing β-phthalimidopropiophenone. Recrystallization from absolute ethanol gave a 79% yield; m.p. 152°.

Anal. Calc'd for $C_{17}H_{12}ClNO_3$: N, 4.67 Found: N, 4.39.

p-Chloro-β-aminopropiophenone hydrochloride (SN-14,036.). The hydrolysis of the phthalimido compound was carried out as previously described for the *p*-tolyl analog. The time of reflux was shortened to twelve hours. The product was crystallized from absolute ethanol; yield 61%; m.p. 219°

Anal. Calc'd for $C_9H_{10}ClNO$ HCl: Cl^-, 16 11. Found: Cl^-, 16.13.

Tri-[β-(p-chlorobenzoyl)ethyl]amine by autocondensation of β-amino-p-chloropropiophenone. One gram of the free base was heated at 80–82° for three hours. Crystallization of the resulting pale yellow solid from methanol gave 0.5 g. of a white crystalline solid; m.p. 148–149°. A mixture melting point with the by-product (m.p. 147–149°) from the condensation below showed no depression. Further recrystallization from ethanol gave a product melting at 154–155°.

Anal. Calc'd for $C_{27}H_{24}Cl_3NO_3$: C, 62.74; H, 4.68; N, 2.71.
Found: C, 62.55; H, 4.70; N, 2.70.

(+)-p-Chlorophenylpantothenone (SN-13,776). The condensation of 6.2 g. of β-amino-*p*-chloropropiophenone and 3.8 g. of the (−)-lactone was carried out as previously described in the preparation of (−)-phenylpantothenone. The usual purification procedure gave 8 g. of a viscous oil which contained small amounts of a waxy solid. This solid by-product (m.p. 147–149°, approx. 1.5 g.) was separated by dissolving the mixture in hot methanol, cooling, and filtering. Removal of the methanol by evaporation under reduced pressure gave 6 g. (43%) of a viscous orange oil; $[\alpha]_D^{20} +25.7°$ (c = 2.456) in absolute ethanol.

Anal. Calc'd for $C_{15}H_{20}ClNO_4$: C, 57.23; H, 6 37; N, 4.45.
Found: C, 58.76; H, 6.19; N, 3.98.

2-Methyl-β-4,5-trichloropropiophenone. Seventy-five grams of β-chloropropionyl chloride was added dropwise to a mechanically stirred mixture of 87 g. of 3,4-dichlorotoluene and 70 g. of powdered anhydrous aluminum chloride. The temperature of the reaction mixture was maintained at 80–90° during the addition and for two hours afterwards. Upon hydrolysis with an ice-hydrochloric acid mixture, the crude product was extracted into 800 ml. of ether. This solution was washed with water and dried over sodium sulfate. Removal of the ether gave 106 g. (78%) of an oil which was used without further purification (the assumed orientation here is based on analogy to the acetylation reaction, where rigorous structural proof has been obtained (15)).

The *2,4-dinitrophenylhydrazone*, made in the usual way, melted at 285° after crystallization from dioxane.

Anal. Calc'd for $C_{16}H_{13}Cl_3N_4O_4$: N, 12.97. Found: 12.92.

4,5-Dichloro-2-methyl-β-phthalimidopropiophenone. An intimate mixture of 106 g. of crude 2-methyl-β-4,5-trichloropropiophenone and 65 g. of potassium phthalimide was heated at 145° for one hour. A mixture of 600 ml. of acetone and 1000 ml. of benzene was added to the resulting melt. The potassium chloride was removed by three extractions with water. After drying over sodium sulfate, the solution was concentrated to a volume of 200 ml. The phthalimide which separated was removed and sufficient ethanol was added to give a slightly turbid solution. After standing for three hours the product was separated; a second crop was obtained by concentrating the filtrate; total yield after crystallization from ethanol, 22 g. (14%); m.p. 123–124°.

Anal. Calc'd for $C_{18}H_{13}Cl_2NO_3$: N, 3.87. Found: N, 3.88.

β-Amino-4,5-dichloro-2-methylpropiophenone hydrochloride. The above phthalimido compound was hydrolyzed, using essentially the procedure of Davies and Powell (5). The time of reflux was increased to 35 hours; yield 62%; m.p. 184–185° after crystallization from absolute ethanol.

Anal. Calc'd for $C_{10}H_{11}Cl_2NO\cdot HCl$: C, 44.76; H, 4.48; Cl^-, 13.18.
Found: C, 44.64; H, 4.58; Cl^-, 13.32.

(+)-4,5-Dichloro-2-methylphenylpantothenone (SN-9973). The procedure used in preparing (−)-phenylpantothenone was again modified slightly. The initial condensation time was increased to seventeen hours. The final product (an oil) was dissolved in a small volume of ethanol and filtered from a small amount of insoluble amorphous solid. Removal of the ethanol by evaporation under reduced pressure and subsequent evacuation using a "hyvac" pump for sixty hours gave a very viscous oil; yield 40%; $[\alpha]_D^{23}$ +17° (c = 1.745) in absolute ethanol.

Anal. Calc'd for $C_{16}H_{21}Cl_2NO_4$: C, 53 01; H, 5.83; N, 3.87.
Found: C, 53.77; H, 5.02; N, 3.51.

dl-N-Pantoyl-β-phenylethylamide (SN-14,254). A mixture of 9.3 g. of β-phenylethylamine and 10 g. of *dl*-pantolactone was heated at 82° for three hours. The straw colored product crystallized slowly on standing at room temperature for two days. Two recrystallizations from butanone-ligroin gave 13 g. (68%) of a white crystalline product; m.p. 92–93°.

Anal. Calc'd for $C_{14}H_{21}NO_3$: C, 66.89; H, 8.42. Found: C, 66.49; H, 8 07.

(+)-N-Pantoyl-β-phenylethylamide. A mixture of 9.6 g. of (−)-pantolactone and 9 g. of β-phenylethylamine was heated at 82° for three hours. The viscous oily product was dissolved in 80 ml. of butanone and 100 ml. of ligroin was added This solution was cooled to 0° and crystallization was induced by scratching the walls of the beaker. Several crystallizations in this fashion gave 8 g. (42%) melting at 72–74°; $[\alpha]_D^{27}$ +44.8° (c = 2.052) in absolute ethanol.

Anal. Calc'd for $C_{14}H_{21}NO_3$: N, 5.58. Found: N, 5 54.

(−)-N-Pantoyl-β-phenylethylamide. This compound was prepared from the (+)-lactone using the same procedure employed in the preceding experiments; m.p. 72–74°; yield 60%; $[\alpha]_D^{27}$ −45.9° (c = 2.047) in absolute ethanol.

Anal. Calc'd for $C_{14}H_{21}NO_3$: N, 5.58. Found: N, 5.59.

A mixture of 0.50 g. of the (−)-butyramide (above) and 0.50 g. of the (+)-butyramide was dissolved in 15 ml. of butanone. This solution was diluted with 35 ml. of ligroin and cooled to 0°. The white crystalline precipitate was removed by filtration. It melted at 92–93° and was identical with the previously prepared *dl*-compound as shown by a mixture melting point.

β-Aminopropiophenone hydrobromide. This compound (m.p. 216–218°) was prepared from phenacyl bromide in 85% yield through the hexamethylenetetramine addition compound in the manner of Mannich and Hahn (16). This procedure gave a much better yield than either of two alternate methods, namely, the treatment of phenacyl bromide with excess ammonia in alcohol (17), or the Gabriel synthesis using potassium phthalimide (2).

N-(Benzoylmethyl)caproamide. To a solution of 6.3 g. of α-aminopropiophenone hydrobromide in 50 ml. of water was added with efficient stirring 6.8 g. of caproyl chloride and then 20 ml. of 30% potassium hydroxide. A red oil separated and solidified after an additional hour of stirring. Crystallization from ethanol gave 2 g. (29%) of a white solid; m.p. 75–77°. An additional crystallization from hexane-ether gave long white rods; m.p. 76–77°.

Anal. Calc'd for $C_{14}H_{19}NO_2$: N, 6.01. Found: N, 5.82.

SUMMARY

The following variations from the phenylpantothenone structure were made to test the effect on antimalarial activity:

(a) The (−)-phenylpantothenone was made of configuration opposite to that of natural pantothenic acid.

(b) The caproyl and α-hydroxycaproyl analogs were synthesized and the latter, N-(2-benzoylethyl)caproamide, was reduced to the corresponding alcohol.

(c) An attempt was made to condense the pantolactone with α-aminoacetophenone.

(d) The pantoyl amide of β-phenylethylamine was made in *d*, *l*, and *dl* forms.

(e) The 4-methyl-, 4-chloro-, and 4,5-dichloro-2-methyl analogs of phenylpantothenone were prepared, only the former being obtained in crystalline form. By-products were shown to be autocondensation products of the β-aminopropiophenones used.

(f) *p*-Tolylpantothenone was reduced to the alcohol *p*-tolylpantothenol. Hydrolysis of this gave pantolactone and γ-(4-methylphenyl)allylamine, the structure of which was demonstrated by synthesis through reduction of β-amino-*p*-methylpropiophenone, followed by dehydration.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

A NEW METHOD OF PREPARING SUBSTITUTED VINYL COMPOUNDS. DEPOLYMERIZATION STUDIES ON VINYL POLYMERS.[1, 2]

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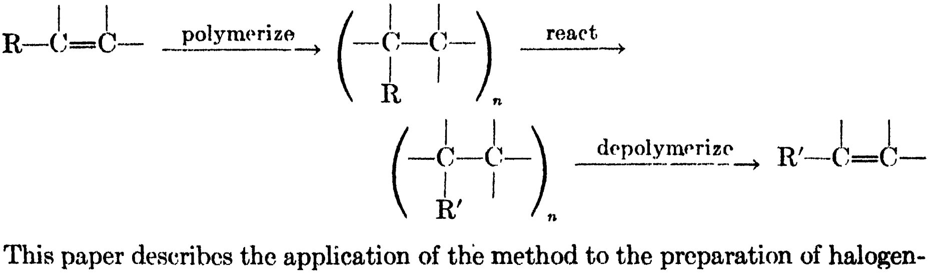
The depolymerization or "cracking" of polyvinyl compounds to simple monomers has long been known and has proved useful in the determination of structures of polymers and in the recovery of scrap in the plastics industry. However, systematic study of the process has not been exhaustive either as regards its theory, practice, or implications in chemical synthesis. The present investigation was undertaken with the object of developing a new method for synthesizing substituted vinyl compounds by altering polymers chemically and then depolymerizing them.

The chemical alteration of vinyl polymers has been frequently studied and applied industrially, but in general the products have been used as such rather than as sources of monomers. The new method makes available certain substitution products which cannot be made directly from monomeric vinyl compounds because of the great reactivity of the double bonds present in them. Essentially it involves protection of such bonds from chemical attack by converting them to saturated polymers followed by regeneration of the double bonds through depolymerization.

One type of application of the method may be illustrated by the following equations:



$$R{-}\overset{|}{C}{=}\overset{|}{C}{-}\xrightarrow{\text{polymerize}}\left({-}\underset{R}{\overset{|}{\underset{|}{C}}}{-}\overset{|}{\underset{|}{C}}{-}\right)_n\xrightarrow{\text{react}}\left({-}\underset{R'}{\overset{|}{\underset{|}{C}}}{-}\overset{|}{\underset{|}{C}}{-}\right)_n\xrightarrow{\text{depolymerize}}R'{-}\overset{|}{C}{=}\overset{|}{C}{-}$$

This paper describes the application of the method to the preparation of halogenated styrenes and related aromatic vinyl compounds. Such substances have attained considerable interest recently in the synthetic rubber and plastics industries.

Depolymerization of high polymers. The application of energy in the form of

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[1] Read before the Organic Section at the Chicago Meeting of the American Chemical Society, September 1946.

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heat, light, audible, and ultrasonic vibrations, mechanical deformation, and chemical reagents causes high polymers to be degraded, but heat alone is the only practical means for accomplishing complete depolymerization. Polymers vary considerably in the temperature at which depolymerization sets in and in the yields of the desired monomer obtainable from them. In general, structures containing quaternary carbon atoms (or hetero atoms) in the polymer chain are more readily and more perfectly depolymerized than other structures. Thus polymethacrylates (or polyoxymethylenes) depolymerize to the corresponding monomers much more satisfactorily than polyacrylates. Nevertheless chains containing tertiary and secondary carbon atoms may be cracked in varying yields to the corresponding vinyl monomers. The polymerization-depolymerization reaction must be considered as essentially an equilibrium reaction. Since energy is evolved in polymerization, it is evident that depolymerization will be favored by supplying energy to the polymer. The energy of activation for the polymerization of styrene is about 30 Cal. while the value for the depolymerization of polystyrene has recently been given as 21.9–23 Cal. (1). Equilibrium reactions which differ in activation energies by 7–8 Cal. may be considered reversible. It should be noted, however, that depolymerization probably proceeds by the breaking of bonds at random postions in the polymer chain while polymerization probably involves the addition of monomer units to the ends of the growing polymer chains. In this sense depolymerization is not strictly the reverse of polymerization. Kinetic treatments of depolymerization reactions have been based on statistical analyses, usually under the assumption that all bonds connecting monomeric units have the same probability of being broken (2). All such treatments ignore secondary reactions arising from the breaking of other bonds than those connecting monomer units and free radical reactions leading to the formation of complex products. It is evident, however, from the poor yields of monomers obtainable from many polymers that such secondary reactions are often important or even predominant in the cracking process.

An attempt was first made to determine the conditions which influence the yield of monomers obtainable on depolymerization and to arrive at a procedure which gives high yields. The following factors were found to be important: (a) the chemical structure of the polymer, (b) its method of formation, (c) its molecular weight, (d) the rate and temperature of cracking, (e) the effect of catalysts, (f) the recracking of partially cracked material, and (g) the use of inhibitors to prevent repolymerization of the monomer.

The effect of chemical structure on the yield of polymer may be seen in Table I. These data were all collected under similar depolymerization conditions. It is interesting to note that the copolymer of styrene with methyl methacrylate gave only fair yields of styrene although polymethyl methacrylate alone depolymerizes in very much better yields than does styrene itself. The styrene-maleic anhydride copolymer gave even poorer yields of styrene.

The method of formation of a polymer seems to be important. Thus there is every reason to suppose that poly-α-methylstyrene would depolymerize in better yields than polystyrene because of the quaternary carbon atoms in the chain. However, α-methylstyrene cannot be polymerized under the usual conditions employed for styrene. Instead of peroxides, strong acids are used as catalysts (3). The polymer contains substantial amounts of a saturated dimer (4) and may differ materially from polystyrene in its structure. Unfortunately we have not yet had an opportunity to examine the higher polymers of α-methylstyrene reported recently by Hersberger, Reid, and Heiligmann (5). Polystyrenes prepared in carbon tetrachloride gave low yields of monomer. Quantities of hydrogen chloride were evolved in these depolymerizations indicating that the solvent had entered the polymer (6).

The influence of molecular weight on cracking yields is closely associated with, and possibly inextricably entangled with, the influence exerted by the method of formation of the polymer. This is so because low molecular weight polymers are obtained by the use of conditions (solvent, temperature, type of catalyst, etc.) which probably alter the structural nature of the polymer.[4] From our studies it would appear that the higher polymers (M.W. > 20,000) give better yields of monomer than the lower polymers (M.W. < 20,000). We are not prepared to say whether the molecular weight alone is responsible for this difference. In Table II are shown monomer yields from polymers of varying molecular weights. All other factors have been arbitrarily excluded.

TABLE I

EFFECT OF CHEMICAL STRUCTURE ON MONOMER YIELDS

POLYMER	MONOMER YIELD, %
Methyl methacrylate	90–95
α-Methylstyrene[a]	18–19
Dichlorostyrene[b]	60–70
m-Trifluoromethylstyrene[c]	65
Styrene	60–65
Styrene-maleic anhydride[d]	11–12
Styrene-methyl methacrylate[d]	66

[a] This is a low M.W. polymer obtained by treatment of α-methylstyrene with conc'd. H_2SO_4 at 0°.

[b] Obtained by bulk polymerization of monomeric dichlorostyrene supplied by Mathieson Alkali Works, Inc., Niagara Falls, New York.

[c] Preparation to be described in a forthcoming publication.

[d] Copolymers; the yields are calculated on the basis of styrene obtained to styrene present in the polymer.

Rapid, high-temperature heating of polymers seems to give better yields of monomers than slow heating at lower temperatures. Under the latter conditions products of complex structure become stable and are formed along with the monomeric styrene. They are not readily depolymerized to styrene. This was clearly shown by an experiment in which polystyrene was heated in an autoclave at 400° for 12 hours. On opening the bomb no styrene was found to be present and none could be obtained from the brittle, glassy product under the usual depolymerization conditions. This indicates that monomer formation is accompanied or followed by other reactions leading to products of intermediate molecular weight which behave on heating quite differently from the original polymer. It is these competitive reactions which are a primary factor in limiting the yields of monomer obtainable from a given polymer, and which make it important to depolymerize and remove the monomer from the high temperature zone as rapidly as possible.

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[4] See Bartovics and Mark, (7) for the effect of temperature of polymerization on the viscosity behavior of polystyrene.

Various methods have been proposed for achieving the preferred conditions of depolymerization. Thus an inert diluent such as sand is added to improve the heat transfer and avoid caking (8), or a molten metal or fused salt bath is used (9), or the polymer is cracked with superheated steam (10). In our hands none of these has proved especially advantageous on quantities of a kilogram or less of polymer. Many cracking procedures lead to compounds which boil near styrene but differ from it structurally. Careful fractionation is necessary in such cases to determine the actual yield of the desired monomer.

TABLE II

EFFECT OF MOLECULAR WEIGHT ON MONOMER YIELDS OF POLYSTYRENES

POLYMER	VISCOSITY M W [a]	MONOMER YIELD, %
A-24	3680	52
A-22	4670	48
A-20	5700	49
A-1	7000	31
Styron	37,000	62
A-13	60,000	55
Lustron	74,000	62
A-18	169,500	62
A-2	190,000	63
A-28	very high[b]	67

[a] The Staudinger equation was used. A k = 1.8×10^{-4} was employed.

[b] This was a bulk polymer formed by allowing styrene to stand at room temperature without catalysts for several months. Its M W. was not determined but was undoubtedly over 200,000.

All catalysts and diluents added to the polymer in the hope of increasing the yields of monomer either were without any effect (alumina, sand, sodium hydroxide, iron filings, steel wool, ceresin wax, Silicone fluid), or materially decreased the yield (aluminum chloride). Catalysts of the sort used in cracking petroleum would be expected to accelerate other types of cleavage than simple depolymerization. Greensfelder and Voge (11) have recently called attention to some of the differences between thermal and catalytic cracking of paraffins which illustrate this point.

A cracking system designed to return the partially cracked products to the cracking pot gives no better yields than otherwise, but the monomers are more readily purified by redistillation. An oxygen-free atmosphere in the cracking equipment and the addition of inhibitors to the receiving flask materially reduce the tendency of the cracking distillate to repolymerize. We were unable to detect an appreciable advantage in cracking polystyrenes under reduced pressure, although higher-boiling monomers such as the chlorinated styrenes were obtained more smoothly and in better yields under such conditions.

The most satisfactory method found for laboratory scale depolymerizations was to heat the polymer in a flask as rapidly as possible with two Meker burners. The flask was attached to a heated packed column (Fig. 1) which served to return the partially cracked vapors to the pot. Above the column was a condensing system adapted to handle large volumes of distillate without flooding. In this equipment 1 kg. of styrene could be cracked in 90 minutes with yields of 60–65%. The yields were determined on carefully fractionated material.

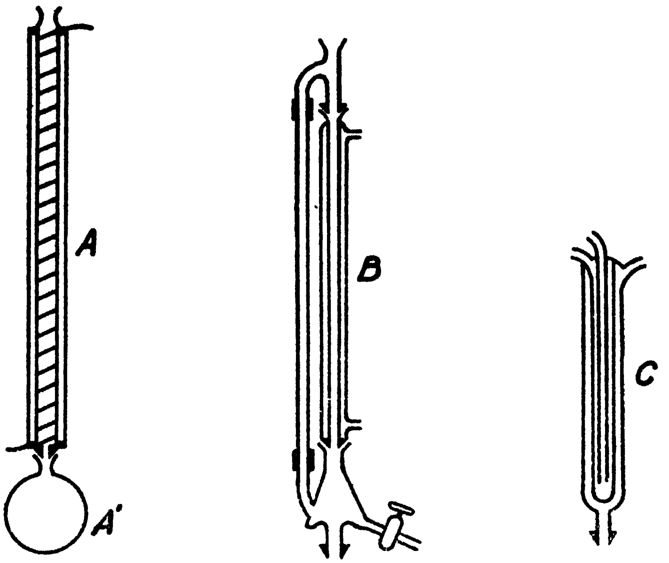

FIG. 1. COLUMN CRACKING UNIT
In operation C fits into the top of B and B into the top of A.

Chemical reactions of aromatic polymers. Polystyrene has been sulfonated (12), nitrated (13), and chlorinated (14). We have reexamined each of these reactions and have in addition studied the bromination and the alkylation of polystyrene under Friedel-Crafts conditions. Only the halogenation products can be depolymerized satisfactorily. Sulfonated polystyrene chars on heating while nitrated polystyrene explodes. The alkylation product cracks to give a complex mixture of products which contains little or none of the desired substituted styrene. Apparently aluminum chloride, even in amounts of 1–2%, causes extensive rearrangements of polystyrene. We have also chlorinated poly-α-methylstyrene and polyindene. Neither of these products gives as good results on depolymerization as do the corresponding styrenes.

Chlorination of polystyrene. The general procedure employed was as follows: polystyrene, dissolved in a suitable solvent, was chlorinated under conditions favoring nuclear substitution; after precipitation and removal of solvent the chlorinated polymer was cracked by heating, and the product was collected and purified by distillation.

A commercial polystyrene of low molecular weight (Dow *Styron* YA5K27) and one of high molecular weight (Monsanto *Lustron* Molding Powder) gave about the same yields of styrene on cracking, but the polymer of low molecular weight was preferable because it required less solvent during chlorination. The solution of the high molecular weight polymer was so viscous that it was difficult to pass chlorine into it.

Suitable solvents for the chlorination of styrene polymers seem to be restricted to chlorinated hydrocarbons. Other solvents either do not dissolve polystyrene and chlorinated polystyrene, or are themselves attacked by chlorinating agents. Carbon tetrachloride, which can be used for very low molecular weight polymers is unsuitable for polystyrenes of molecular weights of 50,000 or higher, which includes nearly all commercial polystyrenes. Tetrachloroethane or chloroform can be used for polymers of high molecular weight. The product prepared using tetrachloroethane solvent gave slightly better yields of mixed monomers than did the product chlorinated in chloroform; however, chloroform was much easier to remove from the polymer. Chlorinations of aqueous emulsions of polystyrene were unsuccessful, for the polymer precipitated before sufficient chlorination could take place. Emulsion polymers were prepared using a wide variety of cation and anion active emulsifying agents, but in every case the polymer precipitated very soon after chlorination was started.

Despite the use of low temperatures, darkness, and halogen carriers, some side-chain chlorination always resulted, for hydrogen chloride was evolved on cracking. It may be that nuclear positions in polystyrene are sterically hindered to a considerable degree, thus favoring side-chain chlorination.

Since many substances are formed in the cracking of chlorinated polystyrene, it was necessary to use good rectification in order to separate and identify the products. Relatively inefficient laboratory columns (6 theoretical plates) did not give entirely satisfactory separations. However, if a very efficient column (100 theoretical plates) was used, the distillation proceeded so slowly that most of the dichlorostyrene polymerized in the still pot. This was true even though the rectification was done under vacuum in an inert atmosphere (nitrogen), and in the presence of polymerization inhibitors. Less trouble was experienced in this respect with monochlorostyrenes than with dichlorostyrenes. Both the mono- and the di-chlorostyrenes polymerize more rapidly than styrene itself.

The fractionated monomers were shown by chlorine analyses, refractive indices, and permanganate oxidations to the corresponding chlorinated benzoic acids, to be principally *p*-chlorostyrene and 3,4-dichlorostyrene. From runs with about twice as many moles of chlorine as styrene, the mixture of monomers contained about 10% of *p*-chlorostyrene, 20–25% of dichlorostyrenes (principally the 3,4-isomer), and 15–20% of unidentified but volatile chlorinated products. All of the monomers, separately or mixed, polymerized readily in the presence of peroxide catalysts to give clear polymers of high molecular weight. In the regular GR-S rubber formulas, excellent elastomers were obtained, but the polymerization rates were lower than those with dichlorostyrenes prepared by other methods. Apparently the present process introduces inhibitors which are not readily removed by simple distillation.

Bromination of polystyrene. The procedure was similar to that used in the chlorination. It was possible to obtain *p*-bromostyrene in 23% yields by the monobromination of polystyrene in carbon tetrachloride followed by cracking of the product. However, even when a considerable excess of bromine was used, it was not possible to obtain a dibromostyrene in this manner. All brominations were run at room temperature, in the dark, and in the presence of iron catalyst. After the bromine had been added, the mixtures were allowed to stand several days to favor completion of the reaction. A bromination with liquid bromine and no other solvent was unsuccessful. Even finely powdered polymer agglomerated to an undissolved mass which the bromine did not penetrate.

Chlorination of poly-α-methylstyrene and polyindene. Since the unsubstituted polymers of α-methylstyrene and indene depolymerize in poor yields (both around 15–20%), it was not anticipated that the halogen substituted polymers would give good yields of monomers. Actually dichlorinated poly-α-methylstyrene gave about 6% yields of 3,4-dichloro-α-methylstyrene while dichlorinated polyindene gave 15% yields of a product whose structure was not determined but which boiled in the range to be expected for the isomeric dichloroindenes.

Conclusions. It is believed that the preparation of substituted vinyl compounds by chemically altering and then depolymerizing the corresponding vinyl polymer offers certain advantages and is a broadly applicable synthetic method. Obviously there are other types of chemical alterations and other types of polymers to which the general method may be applied besides those employed in this investigation. It is our hope to examine some of these possibilities in the near future.

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EXPERIMENTAL

Throughout this part, the letter A refers to polymers, and B to reactions with polymers.

Polystyrenes. In addition to Dow Styron YA5K27 (M.W. 50,000) and Monsanto Lustron Molding Powder (M.W. 74,000) a number of other styrene polymers were studied. The methods of preparation and cracking characteristics of some of them are shown in Table III.

Chlorination of polystyrenes. The chlorination equipment used in the beginning of the work consisted merely of a 76 x 5-cm. tube fitted with a condenser leading to a gas trap, an inlet tube with a fritted glass disk, and a thermometer well. The progress of the chlorination was followed by weighing the chlorination tube at various intervals. The capacity of the tube was small, however, and for larger scale preparations it was necessary to use a three-necked flask or a 120 x 10-cm. tube cooled by an ice-bath contained in a 15-cm. steel pipe closed at the bottom by a welded steel plate 25 cm. square. Eventually six of these latter units were operated simultaneously. The amount of chlorine to be introduced was measured volumetrically in liquid form into a test tube and allowed to evaporate through a fritted glass inlet. A more satisfactory and convenient method was to use a small chlorine bomb which could be weighed from time to time during the chlorination, and the weight of chlorine determined by difference.

After halogenation it was necessary to remove the solvent and dry the chlorinated polymer to constant weight. A convenient method of precipitation consisted in adding the polymer solution to well-stirred alcohol. If the precipitation was done slowly, using solutions containing less than 10–15% of polymer, the product obtained was usually light colored

TABLE III

PREPARATION AND CRACKING CHARACTERISTICS OF POLYSTYRENES

RUN NO.	MONOMER, ML.	SOLVENT, ML.	CATALYST, G.	EMULSIFYING AGENT, G.	TEMP, °C.	TIME, HRS.	VISCOSITY M.W.[a]	CRACKING YIELD, %[b]
A-0	Styrene 780	Dioxane 1500	Bz_2O_2 3.5		100	48	20,000	
A-1	Styrene 4000	CCl_4 3800	Bz_2O_2 12.2		85	22	7,000	31
A-2	Styrene 700	Water[f] 6000	H_2O_2 12.6	Soap 30	60	25	190,000	63
A-3	Styrene 700	Water[f] 6000	H_2O_2 12.6	Stearonyx 15	60	40		65
A-10	Styrene 345 M.M.A.[c] 310	Water[f] 6000	H_2O_2 12.6	Stearonyx 15	60	44		47
A-13	Styrene 750	Water[f] 6000	H_2O_2 36.6	Tergitol 4[i] 158	80	10.5	60,000	55
A-17	Styrene 700	Water[f] 6000	H_2O_2[g] 19.5	Soap 30	50	36		54
A-18	Styrene 520	None	Bz_2O_2		60	96	169,500	62
A-20	Styrene 520	CCl_4 1040	Bz_2O_2 15.6		60	150	5770	49
A-22	Styrene 520	CCl_4 1040	Bz_2O_2 46.8		60	150	4670	48
A-24	Styrene 520	CCl_4 1040	Bz_2O_2 78.0		60	150	3680	52

TABLE III—*Concluded*

RUN NO	MONOMER, ML.	SOLVENT, ML	CATALYST, G.	EMULSIFYING AGENT, G.	TEMP., °C	TIME, HRS.	VISCOSITY M W.[a]	CRACKING YIELD, %[b]
A-26	Styrene 312 M.A.[d] 294	Benzene 1380	Bz_2O_2 12.1		80	24		12[h]
A-30	Styrene[e] 50	Water 150 Glycerol 150	Bz_2O_2 0.5		90	5		56
AL	Lustron						74,000	62
AS	Styron YA5K27						50,000[i]	62

[a] Staudinger equation used.
[b] Average values.
[c] M.M.A. is methyl methacrylate.
[d] M.A. is maleic anhydride.
[e] A pearl polymer.
[f] The emulsion polymers were coagulated with salt and acid before cracking.
[g] Lauryl mercaptan 12.6 g. was added to determine whether it might exert a desirable modifying action.
[h] Yield of styrene. The maleic anhydride was largely decomposed and carbon dioxide was evolved in large quantities
[i] Data on M W. provided by company supplying product.
[j] A 22% aqueous solution.

and free from mechanically entrained impurities. However, the method was not practicable on a large scale because it was time consuming and required a large ratio of alcohol to solvent. It was found that steam distilling the solution of the polymer or adding the solution slowly to boiling water gave a satisfactory separation of polymer and solvent. The polymer was collected by filtration, washed with alcohol, and dried at 110°. This was the procedure used for precipitating the product of large scale chlorinations which were run in chloroform or carbon tetrachloride. When the higher-boiling tetrachloroethane was the solvent, precipitation from hot water failed, for the polymer usually agglomerated, remained sticky, and retained solvent. Alcohol precipitation was used for these polymers. If the alcohol wash was omitted for the polymers precipitated in hot water, the product was very difficult to dry.

The more significant experiments are summarized in Table IV.

The distillates (containing inhibitor) from a number of cracking operations were fractionated in a 75-cm. glass helices packed column at 2.5–5 mm. pressure several times. The products obtained were as follows: (a) *p*-Chlorostyrene, yield 10%. The purest sample showed the properties: b.p.$_{2.5}$ 45.8–45.9°, n_D^{20} 1.5648, d_{25}^{25} 1.090.[5]

Anal. Calc'd for C_8H_7Cl: Cl, 25.6. Found: Cl, 26.3.

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[5] Ushakov and Matuzov (15a) report b.p.$_{2}$ 48.5–49°, n_D^{20} 1.5702, d_4^{20} 1.1143. Brooks (15b) reports b p.$_{3}$ 53–54°, d_4^{20} 1.090, n_D^{20} 1 5658. Both preparations were from *p*-chlorobenzaldehyde *via* *p*-chlorophenylmethyl carbinol.

Oxidation with permanganate yielded *p*-chlorobenzoic acid, m.p. 238–240° (Beilstein, m.p. 242–243°).

(b) 3,4-Dichlorostyrene, yield 25%. The purest sample showed the properties: b.p.$_5$ 81.6–83.5°, n_D^{25} 1.5769.[6]

Anal. Calc'd for $C_8H_6Cl_2$: Cl, 40.9. Found: Cl, 40.2.

Oxidation with permanganate yielded 3,4-dichlorobenzoic acid, m.p. 205.0–205.5.° (Beilstein, m.p. 203–204°).

(c) Intermediate and higher-boiling fractions not further identified, yield 15%.

Synthetic rubbers were prepared from: (a) a mixture of the chlorinated styrenes containing all of the steam volatile fraction from several depolymerization runs, (b) a distillation fraction containing principally monochlorostyrenes, and (c) a distillation fraction containing principally dichlorostyrenes. These rubbers were reported by the General Tire and Rubber Company to compare favorably with rubbers prepared from Mathieson dichlorostyrene. However, the cracked distillates copolymerized more slowly than the commercial product. In seeking to determine where a polymerization inhibitor was being formed in the process a number of experiments were run. It was finally concluded that the inhibitor or its progenitor was formed in the chlorination step.

TABLE IV

CHLORINATION OF POLYSTYRENE AND CRACKING RESULTS

RUN[a] NO.	SOLVENT, L.	CHLORINE, G.	CATALYST, G.	TIME, HRS.	PRODUCT, G.	CHLORINE, %[b]		CRACKING[c] YIELD, %
						A	B	
A1-B4	CCl_4, 2.5	950	$SbCl_5$, 11.7	17	1113	43.4	43.5	36
A1-B5	CCl_4, 2.5	874	I_2, 6	15	1150	45.7		34
A1-B6	CCl_4, 2.5	925	$FeCl_3$, 24	13	1087	42.6	42.2	31
AS-B12	$(CHCl_2)_2$, 2.5	1025	$FeCl_3$, 6	14	1120	44		46
AS-B18	$(CHCl_2)_2$, 4.2	630	$SbCl_5$, 11.7	10	700	40		45
AS-B19	$(CHCl_2)_2$, 2.5	908	I_2, 3	19.5				42
AS-B22	$CHCl_3$, 2.6	1026	$FeCl_3$, 4	18	1004	38		38
AS-B23	$CHCl_3$, 2.7	951	I_2, 3	22.5	984	37		40
AS-B24	$CHCl_3$, 2.7	990	$FeCl_3$, 4 I_2, 1	24.5	976	36		41
Mathieson Dichlorostyrene								75
Monsanto Dichlorostyrene (Styramic HT)								66

[a] In all experiments 624 g. of polystyrene were used except in AS-B18 in which 416 g. were used.

[b] The chlorine content of the polymer was calculated on, (A) the increase in weight of the polymer, and (B) a chlorine determination by analytical methods. Since the two values correspond closely, the analytical determinations were dropped in later experiments.

[c] The cracking yield was determined by distilling the cracked distillate and weighing the fraction boiling 55–120° at 10 mm. pressure.

Bromination of polystryene. Bromine (160 g., 1.0 mole) was added dropwise over a period of four hours to a solution of Dow Styron YA5K27 (104 g., 1.0 mole) in carbon tetrachloride (500 ml.) in which was suspended iron catalyst (2 g.). The mixture was contained in a three-necked flask equipped with a mercury sealed stirrer, condenser, and dropping-funnel. The reaction was run at room temperature, and the mixture was shielded from light. After standing for three days, the product was precipitated in alcohol and dried to constant weight at about 100°. The dried polymer, which was light brown in color, weighed 156 g. A 100-g. sample of this material was cracked at 20 mm. pressure by heating the powder in a flask with a free flame and passing the vapors through a three-foot glass tube, packed with porous plate, heated to 400° in a Carius furnace. The crude slightly reddish cracking distillate weighed 82.5 g. Redistillation gave a crude bromostyrene, b.p.$_{17}$ 85–100°, yield 50%. The liquid was washed with 10% HCl, stirred with Norit and twice distilled. The final pure product was a colorless liquid which readily decolorized bromine and permanganate, yield 25–35%, b p.$_{13}$ 87°, d_{25}^{25} 1.3891, n_D^{25} 1.5850; dibromide m.p. 60.5–61.0°.[7]

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[6] Michalek and Clark (16a) report b.p.$_3$ 76°, d_4^{25} 1.243, n_D^{25} 1.5840. Brooks (15b) reports b.p.$_4$ 69–70°, d_4^{20} 1.256, n_D^{20} 1.5857. Marvel (16b) reports b.p.$_5$ 95°, n_D^{20} 1.5851.

Anal. Calc'd for C_8H_7Br: Br, 46.4. Found: Br, 46.4.

The bromostyrene obtained by this process was further identified by oxidizing a sample with alkaline permanganate to *p*-bromobenzoic acid, m.p. 251–253° (Beilstein 251–253°).

Chlorination of poly-α-methylstyrene. α-Methylstyrene was polymerized by adding dropwise 535 ml. of redistilled monomer (b p. 162–164°) to 600 ml. of conc'd H_2SO_4 at a temperture of −15° to −10°, while using vigorous stirring. The mixture was allowed to stand for three hours at −10° to +10°. The acid layer was decanted, and the sticky orange solid was washed with ice-water and steam distilled, giving about 16 g. of oil and leaving a white sticky polymer as a residue. The oil solidified on standing for 2 days, and was recrystallized from alcohol giving white crystals (m p. 51–52°) which did not decolorize $KMnO_4$ in acetone nor Br_2 in CCl_4. Evidently this is the saturated dimer reported by Tiffeneau (4).

The polymer was chlorinated in CCl_4 solution in the dark at 0–5°, using about 340 g. of polymer, 1500 ml. of CCl_4, and 1 g. of $FeCl_3$. In 20½ hours, 442 g. (6 2 moles) of chlorine was added. The molar ratio of chlorine to monomer was about 2.1 to 1. The mixture was steam distilled to remove the solvent, washed with alcohol, and dried in the oven overnight at 80°. The heat of the oven caused the polymer to darken somewhat It remained sticky and was difficult to dry; yield 450 g. Cracking of this product gave only 6% yields of a mixture of chloro compounds from which was isolated the chief component, 3,4-dichloro-α-methylstyrene, b.p.$_9$ 97–100°, n_D^{25} 1.5746, d_{25}^{25} 1.2675 This compound was also prepared from ethyl 3,4-dichlorobenzoic acid by a method which will be described in a future publication. This sample showed the following constants: b p $_3$ 94°, n_D^{25} 1 5732; d_{25}^{25} 1.2212.

Anal. Calc'd for $C_9H_8Cl_2$: Cl, 37.9. Found Cl, 37 9

Oxidation with permanganate gave 3,4-dichlorobenzoic acid, m p. 205–206° (Beilstein, 203–204°).

3,4-Dichloro-α-methylstyrene is readily copolymerized with butadiene to give excellent rubbers. Like α-methylstyrene it is stable to peroxides when free of other polymerizable substances. This is an advantage in the purification and storing of the monomer.

Chlorination of polyindene. Barrett's Cumar Resin W1, a solid polymer consisting mainly of polyindene with a small amount of polycoumarone, was used in these experiments. The resin (235 g., *ca.* 2 moles of monomer) was dissolved in 1200 ml. of CCl_4 and chlorinated in the dark at 0–10° in the presence of 1 g. of $FeCl_3$. In 6½ hours, 390 g. of chlorine was added. This is an excess of 104 g. over 4 moles. After standing for 36 hours, the mixture was steam distilled, removing the solvent and leaving a fluffy powder which was filtered, washed with alcohol, and dried at 90°. The weight of dried product was 417 g., indicating that 182 g. (5.1 g. atoms) of chlorine had been absorbed. This is slightly over 2.5 atoms of chlorine per indene unit.

The chlorinated Cumar (200 g.) was cracked in the usual manner, giving 53.4 g. of condensate and 95 g. of residue. The condensate was redistilled at 3–5 mm. in a Claisen flask giving three fractions, (a) 75–90°, 15.7 g.; (b) 90–140°, 14.9 g.; (c) 140–260°, 10.4 g. They were not further investigated.

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[7] Ziegler and Tiemann (17a) report for *p*-bromostyrene b.p.$_{11}$ 83.5–84.5°, d_4^{20} 1.401, n_D^{20} 1.5961, dibromide m p. 60–61°. Brown and Nelles (17b) for the same compound report b.p.$_{13}$ 88°, d_4^{20} 1.400, n_D^{20} 1 5933, dibromide m.p. 64°.

Nitration of polystyrene.[8] Polystyrene (5 g.) (M.W. 50,000) was added gradually, with stirring, to 60 ml. of fuming HNO_3 (sp. g. 1.49 to 1.50). The finely powdered solid dissolved almost immediately with the evolution of heat. After the temperature began to drop, the mixture was heated for one hour at 50°. The cooled mixture was poured into about 1½ liters of cold water, giving a pale yellow solid, which was filtered, washed with water, and dried; yield 6.5 g. Nitropolystyrene thus prepared is soluble in nitrobenzene, fuming nitric acid, and conc'd sulfuric acid, but in no other common laboratory solvents. It averages about 9.5–10.0% nitrogen (calc'd for mononitrostyrene 9.4%; for dinitrostyrene, 14.4%). It decomposes without depolymerizing on heating. With fuming nitric acid at reflux temperatures or in a sealed Carius tube at 150° products containing up to 11.22% nitrogen were formed. A dinitropolystyrene could not be obtained even in the presence of conc'd sulfuric acid.

Nitropolystyrenes can be completely reduced to aminopolystyrenes only with considerable difficulty because of the solubility characteristics of the nitro compounds. It is best to use polymers of low M.W. (20,000–50,000) and to reduce an aqueous ammoniacal suspension of the finely divided polymer with sodium hydrosulfite ($Na_2S_2O_4$). In this manner a product completely soluble in dilute acids is obtained.

Finely divided nitropolystyrene, 5 g., was suspended in a solution containing 200 ml. water, 25 ml. conc'd ammonium hydroxide and an excess of sodium hydrosulfite. The mixture was heated three days on a steam-cone, acidified, and the precipitated sulfur removed. The solution was made basic and the polyaminostyrene was filtered off and dried; yield 2.5 g. of a tan colored powder. Aminopolystyrene was not prepared in sufficient amounts to study its depolymerization.

Aminopolystyrenes may be diazotized without difficulty. The diazonium salts couple with phenols and aromatic amines to give yellow and red dyes which are very insoluble in all solvents. Cloth may be dyed by the ingrain method. The colors formed are not greatly different if mordants (tannic acid or tartar emetic) are used and are very fast to washing and solvent action. Diazotized aminopolystyrene was coupled with the following compounds both in solution and absorbed on cotton cloth: β-naphthol—red; Neville and Winther acid—brown-red; Schaeffer's acid—red; α-naphthol—brown; Broenner's acid—brown; dimethylaniline—red in acid, brown in neutral and basic solutions.

Sulfonation of polystyrene. Dow Styron YA5K27 was dissolved in a large excess (10 volumes) of conc'd sulfuric acid by stirring and heating at 100°. The temperature was slowly raised to 160° and heating continued for about eight hours or until a sample of the mixture gave no precipitate when poured into water. The product was cooled, poured into ice and water, neutralized with sodium hydroxide, and evaporated to dryness. The mixture of sodium sulfate and sodium polystyrene sulfonate was ground with potassium cyanide and then heated in the hope that a cyanostyrene would be formed through replacement of the sulfonate group and depolymerization of the product. Only charring resulted and no substituted styrene was obtained.

Alkylation and acylation of polystyrene. Numerous attempts were made to alkylate polystyrene in solution with methyl, ethyl, and propyl halides and to acylate it with acetyl and benzoyl chlorides in the presence of Friedel-Craft type catalysts. Apparently reaction occurred for hydrogen halide was evolved copiously. All attempts to depolymerize the products to the expected substituted styrenes led to complex mixtures. Eventually it was discovered that polystyrene is rapidly degraded and rearranged by aluminum chloride and that cracking in the presence of as little as 1–2% of this catalyst yields very little styrene and gives products boiling over a wide range, which show no unsaturation to bromine or permanganate.

The acylation of styrene itself was recently patented (18). The products were not distilled or carefully purified. Our attempts to prepare acetyl- or benzoyl-styrenes by these and similar procedures yielded polymers on attempted distillation. These were cracked and distillates obtained which did not boil in the right range but which did repolymerize rapidly. Similar results were obtained with α-methylstyrene. It is our belief from numerous experiments that pure alkylated or acylated styrenes cannot be prepared by these methods without considerable modification.

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[8] The preliminary experiments were done in this laboratory by G. M. Steinberg, Latimer Evans, and S. J. Miller. Their contributions are gratefully acknowledged.

Depolymerization experiments. Space does not permit a detailed description of the hundreds of depolymerizations run in the course of this investigation. Instead, general descriptions of the apparatus, techniques, and results not already discussed will be given.

A molten lead depolymerization bath, Fig. 2, similar to the one described by Philip, Stanley, and Wood (9) was constructed. Best results were obtained when the molten metal was held at temperatures of 450–500° and there was vigorous stirring. It was found: (a) that dry, bulk polymer gave better yields than the same polymer in a 10% aqueous emulsion or in a 30% benzene solution, although the liquid forms offered less mechanical difficulties during addition; (b) the yield of cracked distillate (average 80–90%) was considerably higher than the yield of pure styrene (average 60–65%) as determined by fractional distillation through a column; (c) the recracking of products boiling above styrene (so-called dimers, trimers, and tetramers) gave considerable amounts of more volatile materials but very little (2–5%) more styrene; (d) for amounts up to at least 1 kg. other depolymerization equipment is preferable from the standpoint of convenience of operation.

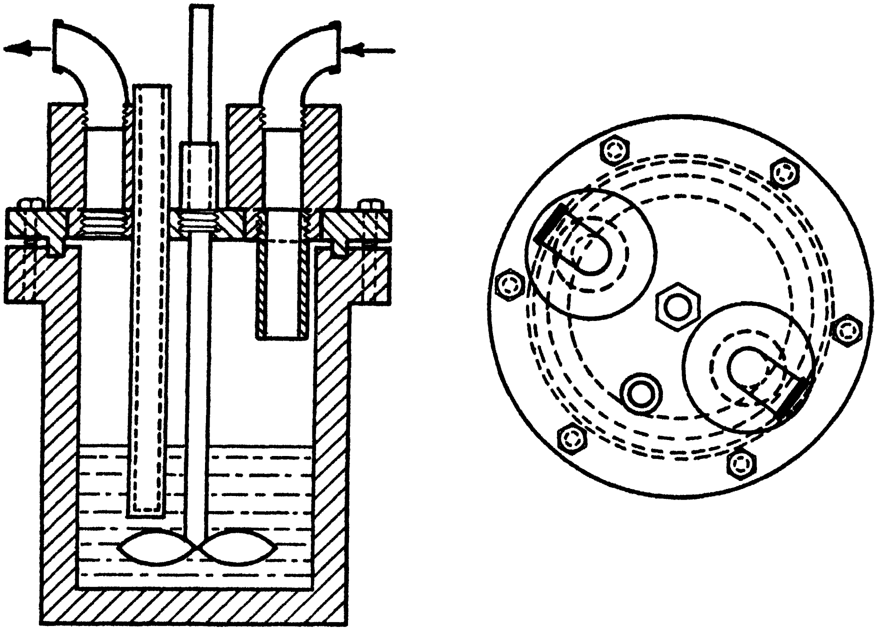

FIG. 2. LEAD BATH CRACKING UNIT

The equipment illustrated in Fig. 1 was simple to operate and gave consistently high yields of monomers which were practically free of high-boiling products. The take-off was adjusted to a 1:1 ratio at the start of a depolymerization when nearly pure monomer was evolved. Later a 3:1 ratio was used to return high-boiling products to the pot. The parallel condenser system avoided flooding and made possible a very rapid cracking rate. The polymer was cracked as rapidly as possible.

The pot A′ was variable in size. Column A was 35 x 460 mm. and was filled with 6–7 mm. glass helices and wound with 20 ft. of No. 24 Nichrome wire which served as a heating unit. Other dimensions are proportional to the illustration and are not especially critical.

SUMMARY

A new method has been developed for synthesizing substituted vinyl compounds which consists in altering polymers chemically and then depolymerizing them. The method has been applied especially satisfactorily to the preparation of halogenated styrenes.

An extensive study of the depolymerization of polyvinyl compounds has been made and factors influencing yields of monomers have been determined.

Lafayette, Ind.

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[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

THE PREPARATION OF 1-METHYL-1-CYCLOHEXEN-6-ONE FROM 1-METHYLCYCLOHEXENE AND FROM CYCLOHEXANE-1,2-DIONE[1]

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1-Methyl-1-cyclohexen-6-one, free from 1-methyl-1-cyclohexen-3-one, was required for combination with butadiene in the preparation of a methyloctalone (1, 2). Ketone of satisfactory quality has been obtained by two routes from cyclohexanone, by fractionation of the products of the action of selenium dioxide on 1-methylcyclohexene in boiling ethanol and by dehydration of the products of the interaction of cyclohexane-1,2-dione and methylmagnesium iodide. It was difficult to get analytically pure ketone by either method, material with carbon content about one per cent too low being obtained each way in about 18% yield based on cyclohexanone. This is suitable for the preparation of the methyloctalone (2). None of the methods described in the literature (Table I) was reported to give so large a yield.

We have found that the 2,4-dinitrophenylhydrazones of 1-methyl-1-cyclohexen-3-one and 1-methyl-1-cyclohexen-6-one can be separated quantitatively by differential adsorption on and elution from alumina, and have shown, by this procedure, that the crude products obtained from selenium dioxide and 1-methylcyclohexene under the conditions we employed contain about 13% of the 3-one.[2] Previous investigators of this reaction (6, 9) have not found 1-methyl-1-cyclohexen-3-one, 3-ol, or 3-yl acetate. The 3-one and two minor components of the crude oxidation product which give colored derivatives with 2,4-dinitrophenylhydrazine can be removed by heating with about one-fourth mole of butadiene at 200° and fractionating the resulting mixture by distillation. Constants for three of these preparations (J, K, L) are given in Table I.

Cyclohexane-1,2-dione, with any enolic form (11, 24), from cyclohexanone and selenium dioxide (12, 13), was allowed to react with methylmagnesium iodide to give 2-hydroxy-2-methylcyclohexanone, or isomeric material, which was converted to semicarbazone without purification. Hydrolysis of the crude semicarbazone with sulfuric acid gave 1-methyl-1-cyclohexen-6-one which may contain 7% of unchanged ketol, since the content of carbon is about one per cent too low for enone. Reconversion of such material to semicarbazone, followed by hydrolysis and repeated fractional distillation, gave a specimen of 6-one with the calculated carbon and hydrogen content. Constants for these preparations are given in Table I (M, N, and O).

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[1] This work was supported by an allotment from the Special Research Fund (Bankhead-Jones Act of June 29, 1935). Not copyrighted.

[2] 1-Methyl-1-cyclohexen-3-one, b_{20} 90–100°, n_D^{25} 1.4920 [Knoevenagel, *Ann.*, **281**, 94 (1894)] was kindly furnished by Mr. W. F. Barthel, Bur. Entomology and Plant Quarantine, for comparison with our material.

The structure of the main product from the reaction between selenium dioxide and 1-methylcyclohexene in ethanol, and the product of dehydration of the ketol described here, is established as 1-methyl-1-cyclohexen-6-one by the following: The methyl group is α to the carbonyl group, since it is α in the methyloctalone formed from the ketone by combination with butadiene (2). The carbon-carbon double bond is in the ring and is α,β to the carbonyl group since the ketone gives an angle-methyloctalone with butadiene (2), absorbs in the ultraviolet like an α,β-enone, and is different from 2-methylenecyclohexanone (14). Confirmation is provided by the identity of the 2,4-dinitrophenylhydrazones with the 2,4-dinitrophenylhydrazone from the ketone from the nitrosochloride of 1-methylcyclohexene, which we prepared according to the procedure of Wallach (4).

TABLE I

PROPERTIES OF 1-METHYL-1-CYCLOHEXEN-6-ONE

PREPN.	REF.	B.P., °C./MM.	n_D	°C.	SOURCE
A	(3)	178–181	1.4831	20	H_2SO_4 on oxime from nitrosate of 1-methylcyclohexene
B	(4)	178–179	1.4833	20	H_2SO_4 on oxime from nitrosochloride of 1-methylcyclohexene
C	(5)	170–171	1.4646	17	Quinoline on 2-chloro-2-methylcyclohexanone
D	(6)	178–179/760 69–70/16	1.4820	22	CrO_3 on an alcohol from 1-methylcyclohexene and SeO_2
E	(7)	69–70/16	?		$KHSO_4$ on a ketol from 1,2-cyclohexanedione and CH_3MgI
F	(8)	?	?		1 Methylcyclohexene and O_2
G	(9)	?	?		SeO_2 on 1 methylcyclohexene in AcOH + Ac_2O
H	(10)	172–176	1.4803		CrO_3 on 1 methylcyclohexene
J[a]		176–178/751	1.4865	21	SeO_2 on 1-methylcyclohexene. Contains 1-methyl-1-cyclohexen-3-one
K[a]		63–69/14	1.4855	20	SeO_2 on 1-methylcyclohexene, then heated with butadiene
L[a]		65/14	1.4850	19.6	K redistilled. See exptl. part for anal. and ultraviolet abs'n
M[a]		176–178	1.4828	20.6	H_2SO_4 on scbzone of ketol. See exptl. part for anal. and UV abs'n
N[a]		66–66.5/14	1.4819	19.8	H_2SO_4 on scbzone. of ketol. See exptl. part for anal and UV abs'n
O[a]		66.9/14	1.4854	22.2	N redistilled. Anal. and ultraviolet abs'n in exptl. part

[a] Present work.

2-Hydroxy-2-methylcyclohexanone, prepared from cyclohexane-1,2-dione and methylmagnesium iodide, has been reported to be a distillable liquid (15, 7). The crude ketol used in the present work is liquid and consists chiefly of material boiling within the previously reported boiling ranges. However, it contains or is readily changed into two other compounds isomeric with hydroxymethylcyclohexanone. One of these is a solid, m. 173.4–174.4°, which crystallizes from distillates of the crude ketol when they have been stored for a week or more, and from distillates recovered after unsuccessful dehydration experiments in which heat and acids were employed. The other isomer, which we have not obtained pure, is a liquid which b. 190–202° at atmospheric pressure. This may have been formed from hydroxymethylcyclohexanone at the temperature required for the distillation (bath 240–250°) , but it also might be formed during distillations at lower temperatures, or even be present in the product from the Grignard reaction. It is suggested, on the basis of comparison with the properties of related ketols (16, 17), that the solid is a dimer and that the liquid b. 190–202° is chiefly 1,2-epoxy-2-methylcyclohexanol.

Conversion of the "ketol" b_{16} 80–95° to enone was attempted by a number of common dehydration procedures, all of which failed. Although some enone was usually formed, much of the "ketol" was recovered unchanged. This stability is understandable if it be assumed that much of the "ketol" exists as the epoxide isomer.

The semicarbazone of 2-hydroxy-2-methylcyclohexanone (15) was obtained from crude undistilled "ketol", from "ketol" which had b_{16} 80–95°, and from the solid isomer. The 2,4-dinitrophenylhydrazone of 1-methyl-1-cyclohexen-6-one was obtained, by the usual procedure, from the solid isomer, and from many distillates from the "ketol". These observations suggested the procedure for the preparation of 1-methyl-1-cyclohexen-6-one from cyclohexane-1,2-dione which was finally developed, hydrolysis of the semicarbazone from undistilled "ketol".

EXPERIMENTAL[3]

1-Methyl-1-cyclohexen-6-one from 1-methylcyclohexene. Previous investigators of the reaction between 1-methylcyclohexene and selenium dioxide have used less than one mole of selenium dioxide in ethanol (6) or in a mixture of acetic acid and acetic anhydride (9) and have obtained 1-methyl-1-cyclohexen-6-ol or the acetate as the chief product. No mention was made of the 3-ol or the 3-one. In the present work 96 g. of methylcyclohexene, b. 110–114°, made from cyclohexanone and methylmagnesium iodide, 250 ml. of ethanol (commercial absolute or recovered from previous batches), and 111 g. of powdered selenium dioxide were mixed and shaken occasionally at 30° in a flask with a reflux condenser. Addition of the dioxide in small portions appeared to give no advantage. The mixture warmed up spontaneously in a few minutes. Sometimes the flask was cooled with water at about 20°, but the reaction could usually be controlled without this. Most of the selenium dioxide did not dissolve. After about an hour, when the mixture had cooled, it was refluxed for four hours in a boiling water-bath. Refluxing was continued for three hours more on the following day The mixture was filtered, the solids washed with ethanol, and the ethanol (with some recoverable 6-one) was removed at the water-pump with a column and bath at 60° Rapid distillation of the residue gave 63 g., $b_{14\text{-}16}$ 62–102°. Redistillation at 14 mm. gave the following fractions: (A) b. 34–66°, 2 g.; (B) b. 66–76°, $n_D^{20.6}$ 1.4856, 30 g.; (C) b. 76–82°, $n_D^{20.6}$ 1.4900, 3 g.; (D) b. 82–105°, $n_D^{20.6}$ 1.5150, 15 g. The content of compounds reacting with 2,4-dinitrophenylhydrazine in these fractions, calculated as dinitrophenylhydrazones (DNPH's) of carbonyl compounds, $C_7H_{10}O$, is about as follows: (B) 89%, (C) 91%, (D) 40%. These values were obtained from the weights of the DNPH's by adding a correction of 5% for incomplete precipitation. The value of the correction was estimated by titrating a typical fraction with hydroxylamine (19). Separation of the products from B and 1.2 equivalents of 2,4-dinitrophenylhydrazine on a column of alumina (see below) and weighing the several eluted components indicated a content of 67.2% 6-one, 12.9% of carbonyl compound II, 9.5% of carbonyl compound III, and 10.4% of non-carbonyl material. In similar work on another fraction which contained only two carbonyl compounds (see below) it was shown that the minor component is 1-methyl-1-cyclohexen-3-one.[3] The yields of material corresponding to B from the next eleven batches were higher, amounting to from 36 to 44 g.

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[3] All melting points are corrected. Microanalyses by Arlington Laboratories, Fairfax, Virginia.

Fraction B mixed with similar cuts, 60.8 g., 6 g. of butadiene, and a few crystals of hydroquinone were heated in a sealed tube under nitrogen for forty hours at 200°. Fractional distillation of the products gave 27.3 g. of 1-methyl-1-cyclohexen-6-one, b_{17} 67–74°, 97% (corrected) pure by the gravimetric DNPH method and free from other carbonyl compounds (alumina column). Finally the distillates from two one-mole batches of selenium dioxide on methylcyclohexene were combined before fractional distillation and a single fraction, corresponding to B + C above, was taken for purification with butadiene; 85 g. of B + C gave 45.3 g., b_{13} 62–69°. n_D^{20} 1.4850, yield 18% on cyclohexanone (17% recovered at this point, to which is added 1% recovered from other fractions; 1-methylcyclohexene from cyclohexanone, 80%). 1-Methyl-1-cyclohexen-6-one of this degree of purity gives the maximum yields of methyloctalone (a 9-methyl-1-octalone with the C-C double bond probably at C-6) and maximum recoveries of unchanged 6-one, thus far observed, when heated with further portions of butadiene (2).

Similar material from another batch, b_{14} 63–69°, n_D^{20} 1.4855 (K, Table I), was twice fractionated by distillation to give: (E) b_{14} 63–65°, $n_D^{19.6}$ 1.4837; (F) (L, Table I) b_{14} 65°, $n_D^{19.6}$ 1.4850, ultraviolet absorption λ_{max}2355 Å (ϵ 9200), λ_{min} 2780 Å (ϵ 9), λ_{max} 3180 Å (ϵ 42);[4] (G) b $_{14}$ 65–66°, $n_D^{19.6}$ 1.4862.

Anal. of Fraction F. Calc'd for $C_7H_{10}O$: C, 76.3; H, 9.15.
Found: C, 74.3; H, 9.1
Found, by a modification of Iddles' (18) (see below) gravimetric DNPH method: methylcyclohexenone, 96.5%.

Estimation of carbonyl compounds $C_7H_{10}O$ in the various fractions. The estimation was usually made by Method 1, which consisted in taking 0.2 g. of the fraction, 28 ml. of ethanol and 0.44 g. (1.2 equivalents) of 2,4-dinitrophenylhydrazine, mixing, bringing to boiling, adding 0.6 ml. of concentrated hydrochloric acid, boiling for ten minutes, allowing to cool, filtering with suction, drying without washing, and weighing. The values so obtained were checked, for some fractions, by two other methods which gave higher values and, therefore, corrections were sometimes applied as already indicated. Method 2 was a modification of that of Iddles (18). About 0.2 g. of the fraction was dissolved in 10 ml. of ethanol and the solution was dropped with swirling into a lukewarm solution of 0.72 g. of 2,4-dinitrophenylhydrazine in 150 ml. of 2 *N* hydrochloric acid. Three more ml. of ethanol was used to complete the transfer of material. Finally 50 ml. more of 2 *N* hydrochloric acid was added and the mixture was allowed to stand at room temperature for four days. The precipitate was filtered, washed with 2 *N* hydrochloric acid and water, and dried at 110–120°. Method 3 was that of Stillman and Reed (19) in which hydroxylamine is employed.

A fraction, which gave a precipitate by Method 1 which could not be separated into components on alumina (K, Table I), was found to contain 92% of methylcyclohexenone by Method 1 and 95.1% by Method 2. Fraction J (Table I) contained, by Method 1, 94% of

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[4] **We are indebted to Mr. Harry Bastron of this Bureau for all the ultraviolet absorption data in this paper.**

TABLE II

Ultraviolet Absorption of Fractions Containing more than 90% 1-Methyl-1-cyclohexen-6-one[a]

SOURCE	SOLVENT	λ_{max} (Å)	ϵ
Nitrosochloride of 1-methylcyclohexene (4)[b]	Hexanes	2280	10600
1 Methylcyclohexene and SeO_2[c]	Hexanes	2270	9600
1-Methylcyclohexene and SeO_2[c]	Water	2400	11000
1-Methylcyclohexene and SeO_2 (L, Table I)	Ethanol	2355	9200
Semicarbazone of 2 hydroxy-2-methylcyclohexanone	Ethanol		
(M, Table I)	Ethanol	2360	9500
(N, Table I)	Ethanol	2355	10000
(O, Table I)	Ethanol	2350	9300

[a] Measurements by Mr. Bastron.

[b] n_D^{21} 1.4812.

[c] Not analyzed. Probably contained 1-methyl-1-cyclohexen-3-one.

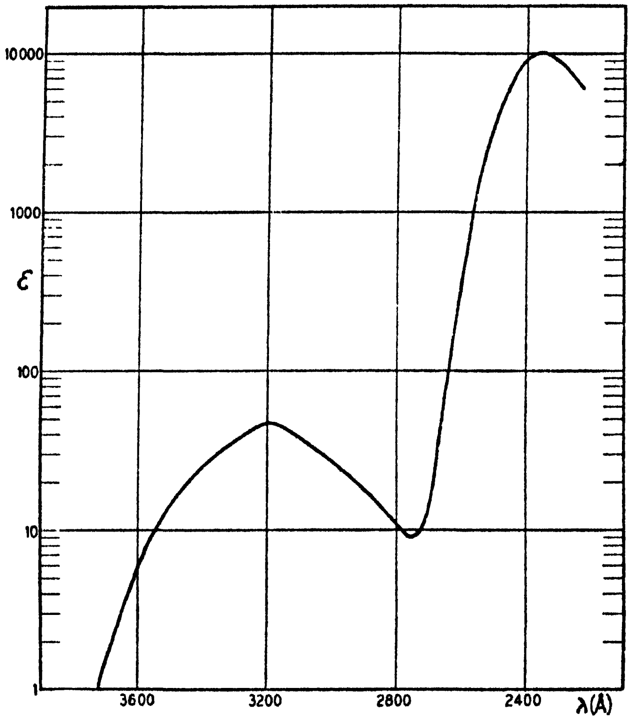

Fig. 1. Absorption Spectrum of 1-Methyl-1-Cyclohexen-6-One (95–98% Pure) in Ethanol

compounds reacting with 2,4-dinitrophenylhydrazine calculated as DNPH's of $C_7H_{10}O$; by Method 3, 98.9–99 3% of carbonyl compounds calculated as $C_7H_{10}O$.

DNPH of 1-methyl-1-cyclohexen-6-one from the products of the interaction of 1-methylcyclohexene and selenium dioxide. The material employed for the identification of the two ketones was obtained by a procedure somewhat different from the preparative procedure already described. The selenium dioxide (111 g.) was added gradually during one hour to 96 g. of 1-methylcyclohexene in 250 ml. of ethanol at 28°. Heat was then applied, cautiously at first, thereafter in amount sufficient to maintain a steady refluxing for six hours. Steam distillation of the products gave four fractions: I, about 300 ml., containing much ethanol; II, about one l.; III, about one l.; and IV, the distillate obtained by taking the residue from III to dryness. After removal of ethanol (and probably 1-methylcyclohexene) from fraction I at 80 mm. and bath 50°, the several fractions were worked up separately by extraction with ether. Thirty-six g. of material b_{25} 77–80° and 20.5 g., b_{25} 90–115° were obtained. The lower-boiling fraction was combined with another portion (32 g.) of similar material. This was twice fractionated by distillation at 754 mm. to give 53 g., b. 176–178° (J, Table I).

Two ml. of J and 1.5 g. of 2,4-dinitrophenylhydrazine gave by Method 1, modified by taking an excess of ketones, 95% of mixed DNPH's, m. 176–178°. Recrystallization from ethanol gave the DNPH of 1-methyl-1-cyclohexen-6-one (6-DNPH), m. 207–210°; mixture with 2,4-dinitrophenylhydrazine (m. 198–199°), m. 173–180°.

Anal. Calc'd for $C_{13}H_{14}N_4O_4$: C, 53.8; H, 4.9; N, 19.3.
Found: C, 53.95; H, 5.0; N, 19.2.

This 6-DNPH was identical with 6-DNPH from the mixture of isomers of 2-hydroxy-2-methylcyclohexanone (see below) on the basis of mixture melting-point and properties of the crystals.[5] It was also identical with the DNPH from 1-methyl-1-cyclohexen-6-one prepared by the method of Wallach (4) (by F. L. Schmehl).

Separation of the DNPH's of 1-methyl-1-cyclohexen-3-one and 1-methyl-1-cyclohexen-6-one on alumina. Mixtures of DNPH's were resolved by differential adsorption by Strain (20). An interesting application is the separation of the DNPH's of estrone and equilenin on alumina (21). 1-Methyl-1-cyclohexen-3-one[3] gave the DNPH, m. 117–173°; Marvel and Levesque (22) found m. 172.5–173°. A solution of 5.6 mg. of this 3-DNPH and 14.6 mg. of 6-DNPH in 75 ml. of petroleum ether (redistilled Skellysolve "B", essentially n-hexane, b 60–70°) was poured on a column of 15 g. of alumina (Merck's according to Brockmann), 8 mm. wide. It formed a band 115 mm. long. Separation into two bands was observed after 150 ml. more Skellysolve "B" had been added. When 175 ml. in all had been added, the lower band reached the bottom of the column. Elution of the two bands separately with Skellysolve "B" was possible.

A mixture of the 3-DNPH with DNPH (yield 92% by method 1; corrected value for ketone content of source fraction, 97%) from the fraction, b_{17} 67–74°, obtained from the products of the reaction of 1-methylcyclohexene and selenium dioxide by removal of some minor components by heating with butadiene as described before, exhibited the same phenomena when dissolved in Skellysolve "B" and chromatographed on alumina. A solution of 3.4 mg. of 3-DNPH and 15.6 mg of this 6-DNPH in 60 ml. of Skellysolve "B" was poured onto a column of 15 g. of alumina, 6 x 460 mm. Development with Skellysolve "B" for about ten hours gave two bands; upper, 113 mm., lower, 176 mm. Elution of the lower band with the same solvent gave 17.1 mg. (6-DNPH, less strongly adsorbed!). Elution of the upper band gave 4.1 mg. of 3-DNPH Other things being the same, a somewhat longer column is required to effect the resolution when the 3-DNPH and 6-DNPH are present in about equal amounts.

Homogeneity of the fraction recovered after heating with butadiene. An experiment was carried out, similar to that described in the preceding paragraph, but with omission of the 3-DNPH. A solution of 20.7 mg. of the DNPH from the fraction b_{17} 67–74° in 60 ml. of Skellysolve "B" was taken. After passing solvent through the column for sixteen hours, there was a single band at the bottom of the column, 304 mm. long. Elution of this material in many small portions, and readsorbing these portions on the column in the order of elution, followed by development with solvent, gave again only one band. Partly resolved mixtures of 3-DNPH and 6-DNPH could be completely resolved by elution and repassage through the column in this way. Heating with butadiene has therefore removed from material similar to fraction B all compounds giving insoluble colored products with 2,4-dinitrophenylhydrazine excepting 1-methyl-1-cyclohexen-6-one. The other data presented indicate that this product, which is typical of the material which has been used for the preparation of the methyloctalone, contains about 5% of non-carbonyl compounds and 95% of 1-methyl-1-cyclohexen-6-one.

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[5] We are indebted to Mr. F. L. Schmehl for the examination of the crystals. It was found that 6-DNPH, 3-DNPH and 2,4-dinitrophenylhydrazine are readily distinguished under a polarizing microscope.

Demonstration of 1-methyl-1-cyclohexen-3-one in fraction J (Table I) from 1-methylcyclohexene and selenium dioxide. A solution of 21.3 mg. of the DNPH from fraction J, not recrystallized, in 75 ml. of Skellysolve "B" was poured onto a column of 15 g. of alumina, 8 mm. wide, through which 25 ml. of solvent had previously been passed. Development with 300 ml. of Skellysolve "B" gave two bands; the upper, 126 mm., the lower, 152 mm. long. Elution of the lower band with the same solvent gave 15.3 mg.; the upper band gave 5.9 mg. The solution of the eluate from the lower band was concentrated and passed through a second column of alumina. There was no further resolution. The solution of the eluate from the upper band was concentrated and to it was added 4.8 mg. of 3-DNPH. This was poured onto a column of alumina and the colored band was brought to the bottom of the column with 800 ml. of Skellysolve "B". There was no separation; hence the upper band from the DNPH's from fraction J consisted of 3-DNPH. Fraction J consists almost entirely of 1-methyl-1-cyclohexen-6-one and 1-methyl-1-cyclohexen-3-one in the ratio of three to one.

Cyclohexane-1,2-dione (mixture of tautomers ?). Cyclohexane-1,2-dione (enol), m. 38–40° (11). Cyclohexane-1,2-dione (mixture of tautomers ?), b_{25} 96–97°, pale green liquid, was obtained from cyclohexanone and selenium dioxide (12, 13) in 19% yield calculated on cyclohexanone taken (these investigators calculated the yield on selenium dioxide taken, to be 35%). This liquid product was obtained after unchanged cyclohexanone had been removed by dissolving the dione in aqueous potassium hydroxide and reprecipitating with hydrochloric acid. In the present work the cyclohexanedione for reaction with methylmagnesium iodide was prepared by mixing 112 g. (one mole) of finely ground selenium dioxide, 500 ml. of ethanol (commercial absolute) and 105 ml. (one mole) of cyclohexanone, shaking thoroughly every half hour for three hours, letting stand sixteen to forty hours, refluxing for four hours, removing the solids by filtration, removing ethanol at 45° with a water-pump through an 85-mm. column, and distilling. Alkali and mineral acid were not used in the purification. Reliance was placed on fractional distillation for removal of most of the cyclohexanone. The fractions b_{17} 78–100° crystallized soon after condensing or when kept at 5° overnight. Redistillation of three such fractions from one-mole batches combined gave 110 g., b_{17} 78–100°, $n_D^{20.6}$ 1.5069. The higher-boiling fractions remained liquid. When these were kept several months and then distilled, about half was recovered as solid (perhaps solid tautomer forms on standing or under conditions of distillation); yield, 36% on cyclohexanone. The refractive index of these fractions, taken before crystallization, was sometimes as low as $n_D^{20.2}$ 1.4955. The yield stated was obtained several times. Yields of 30–33% were obtained many times. For the preparation of one batch of 1-methyl-1-cyclohexen-6-one, once distilled dione was used. This b_{18} 80–100°, n_D^{20} 1.4995, 103.5 g. from two one-mole batches (46%).

2-Hydroxy-2-methylcyclohexanone or isomers. To the Grignard reagent from 52.6 g. of magnesium and 298 g. of methyl iodide in 800 ml of ether, which had been refluxed for two hours, a solution of 112 g. of redistilled solid cyclohexane-1,2-dione in 400 ml. of ether was added slowly during two hours, and the mixture was refluxed for two hours more. The next day it was poured onto ice, acidified with hydrochloric acid, and stirred until clear. On the third day the ether layer was separated and the water layer was saturated with sodium chloride and extracted with 6 portions of ether, 125 ml. each. After concentration to about 400 ml. the combined ether solutions were washed twice with saturated sodium chloride solution (total, 50 ml.) and dried with sodium sulfate. After evaporation of the ether, distillation at 15 mm. gave 95 g., b. 80–95°, $n_D^{20.8}$ 1.4644, and 15 g. of material with higher boiling range and refractive index. The yield of material, b_{15} 80–95°, in two later runs was only 75 g. This point was not investigated because in the subsequent work the crude "ketol" was converted to semicarbazone and 1-methyl-1-cyclohexen-6-one without distilling.

Anal. Calc'd for $C_7H_{12}O_2$: C, 65.6; H, 9.4.
Found, fraction b_{15} 80–95°: C, 66.6; H, 9.7.

This fraction gave the 3,5-dinitrobenzoate, colorless (after Filter-Cel), m. 154–155°, obtained by Wilson and Read (15). The semicarbazone, m. 203–203.5° (15), was prepared by recrystallization of the semicarbazone from crude undistilled "ketol".

Anal. Calc'd for $C_8H_{15}N_3O_2$: N, 22.7. Found: N, 22.6.

One g. of the fraction b_{15} 80–95°, 1.8 g. of 2,4-dinitrophenylhydrazine, and 50 ml. of ethanol were heated to boiling and the solution was made clear by the addition of one ml. of concentrated hydrochloric acid. Boiling was then resumed. No precipitate formed during the first three minutes (in contrast to 1-methyl-1-cyclohexen-6-one), but after five minutes of boiling there was a heavy precipitate of the 2,4-dinitrophenylhydrazone of 1-methyl-1-cyclohexen-6-one; 2 g., after standing two days, m. 198–203°, mixed m.p. with material from products of selenium dioxide on 1-methylcyclohexene, 199–203°. Recrystallized for analysis, m. 205–207°.

Anal. Calc'd for $C_{13}H_{14}N_4O_4$: C, 53.8; H, 4.9; N, 19.3.
Found: C, 53.8; H, 5.0; N, 19.1.

Attempts to dehydrate the distilled "ketol". The fraction b_{15} 80–95°, described in the preceding section, was subjected to a large number of dehydration procedures which did not give 1-methyl-1-cyclohexen-6-one in satisfactory yield. Some reagents gave, along with much unchanged (refractive index) material, products with refractive index as high as 1.500 (n_D enone, see Table I). It is possible that the conditions were so extreme that *o*-cresol was formed. The indices were especially high when iodine was employed for the dehydration.

When 45 g. of "ketol" and 2.5 g. of potassium bisulfate were heated in a bath at 250° for one hour and the products were distilled, it was possible to recover about half the material taken in one fraction, b_{16} 80–90°, $n_D^{20.5}$ 1.4663, λ_{max} (ultraviolet) 2680 Å (ϵ 180), λ_{min} 2500 Å (ϵ 105) in hexanes.

In another trial 30 g. of "ketol" was refluxed with 60 ml. of water and 30 g. of oxalic acid for three hours. All of the "ketol" dissolved and the solution remained nearly colorless. Steam distillation, extraction of the distillate and residue with ether, and fractional distillation of the dried residue from ether gave five fractions (5 ml. each), b_{16} 74–93°, $n_D^{20.6}$ 1.4608–1.4685. A middle fraction, b_{16} 86–87°, $n_D^{20.6}$ 1.4669, was shown by analysis to be nearly pure "ketol". This b. 190–202° at atmospheric pressure; $n_D^{21.4}$ 1.4668.

Anal. Calc'd for $C_7H_{12}O_2$: C, 65.6; H, 9.4.
Found: C, 66.0; H, 9.2.

Absorption in ultraviolet: λ_{max} 2350 Å (ϵ 270); λ_{min} 2500 Å (ϵ 210); λ_{max} 2720 Å (ϵ 330) in ethanol. λ_{max} 2745 A (ϵ 128) has been found (23) for 2-hydroxy-3-methyl-6-isopropylcyclohexanone.

The crystalline isomer of 2-hydroxy-2-methylcyclohexanone. A number of "ketol" preparations, both before and after being subjected to dehydration procedures such as heating with potassium bisulfate, deposited crystals when allowed to stand for a week or more. One fraction b_{12} 74–87°, n_D^{22} 1.4650, deposited crystals after eight days at 0°. The crystalline solid from 66 g. (n_{D}^{20} of residual liquid was 1.4690) was filtered, washed with Skellysolve "F", and recrystallized from Skellysolve "B"; 3.5 g., m. 172.4–173.4°.

Anal. Calc'd for $C_7H_{12}O_2$: C, 65.6; H, 9.4.
Found: C, 65.6; H, 9.5.

This compound dissolved in ethanol was transparent to ultraviolet light, thus indicating the absence of carbonyl and α-ketol groups.

Two hundred mg. of the solid $C_7H_{12}O_2$, 500 mg. of hydroxylamine hydrochloride, 3 ml. of water, and 2 ml. of 10% sodium hydroxide solution were added to enough ethanol to dissolve nearly all of the solid. The mixture was heated at 100° for one hour. The crystals which separated on cooling consisted of unchanged compound, m. 173.4–174.4°. No oxime was found.

Twenty-two ml. of ethanol containing 219 mg. of the solid $C_7H_{12}O_2$ and 420 mg. of 2,4-dinitrophenylhydrazine was brought to boiling, 0.5 ml. of concentrated hydrochloric acid was added, the mixture boiled again, then cooled. The DNPH of 1-methyl-1-cyclohexen-6-one was obtained in 96% yield, m. 207–209°.

Acetylation of 2-hydroxy-2-methylcyclohexanone. "Ketol", b_{13} 69–81°, n_{D}^{20} 1.461–1.466, 25.4 g., and 200 ml. of acetic anhydride were heated at 100° for eleven hours. After removal of acetic anhydride and acetic acid, 22.2 g. of material b_{14} 100–130° (66% calculated as acetate) was recovered. Some solid $C_7H_{12}O_2$, m. 173.5–174.5°, separated from this distillate, indicating resistance to acetylation. Fractional distillation of the acetylation products gave a cut b_{15} 115–118°, $n_{\mathrm{D}}^{20\,2}$ 1.4570.

Anal. Calc'd for $C_9H_{14}O_3$: C, 63.5, H, 8.3.
Found: C, 63.9; H, 8.7.

Attempts to convert the acetate to 1-methyl-1-cyclohexen-6-one in satisfactory yield were not successful.

1-Methyl-1-cyclohexen-6-one from cyclohexane-1,2-dione without purification of intermediates. Redistilled solid cyclohexane-1,2-dione, b_{18} 78–110°, $n_{\mathrm{D}}^{20\,6}$ 1.5069 (110 g.), and methylmagnesium iodide were allowed to react as already described. The products, however, were worked up to the drying of the ether solution inclusive on the second day and a few crystals of sodium thiosulfate were added to the saturated sodium chloride solution used for washing in order to remove traces of iodine. Evaporation of the ether gave 121 g. of crude "ketol", which was dissolved in 120 ml. of ethanol, mixed with 107 g. of semicarbazide hydrochloride and 161 g. of anhydrous sodium acetate in 292 ml. of water, and the mixture was shaken vigorously. Semicarbazone was precipitated almost immediately. Filtration and strong suction on the following day gave about 170 g. which was mixed with one l. of 10% aqueous sulfuric acid and distilled in steam. The distillate was exhaustively extracted with ether, the extract was washed with saturated sodium bicarbonate solution and dried with sodium sulfate, and the ether was evaporated on a steam-bath. Distillation of the residue gave 62 g. (50%), b_{14} 67–69°, $n_{\mathrm{D}}^{20\,4}$ 1.4826, which was combined with 52 g. of similar material and the whole distilled at atmospheric pressure with an eight-inch column. Two cuts of the distillate were examined: (I) 65 g., b. 176–178°, $n_{\mathrm{D}}^{20\,6}$ 1.4828; and (II) 32 g., b. 178–180°, $n_{\mathrm{D}}^{20\,6}$ 1.4838 The ultraviolet absorption data for these and other fractions are given in Table II.[4]

Anal. Calc'd for $C_7H_{10}O$: C, 76 3; H, 9.15.
Found: (I) C, 75.6; H, 9.4.
(II) C, 75.8; H, 9.2.

These values for carbon and hydrogen content correspond to a mixture of 93% methylcyclohexenone and 7% hydroxymethylcyclohexanone. Redistillation of fraction I disclosed that the material was not homogeneous.

Accordingly it seems likely that purer specimens of 1-methyl-1-cyclohexen-6-one might be obtained if the conditions of decomposition of the semicarbazone were altered. A few variations were tried, including refluxing for one hour before steam distillation, without substantial difference in the result. Material from four such experiments, b_{14} 64–72°, n_D^{20} 1.4807 (1.4754–1.4830), was therefore reconverted to semicarbazone and this semicarbazone (largely of methylcyclohexenone) (semicarbazone of 2-hydroxy-2-methylcyclohexanone is white, semicarbazone of 1-methyl-1-cyclohexen-6-one is yellow) again hydrolyzed. Fifty-seven g. in 57 ml. of ethanol was mixed with 61 g. of semicarbazide hydrochloride and 92 g. of anhydrous sodium acetate in 166 ml. of water. The mixture was vigorously shaken, let stand overnight at room temperature, then one day more in the refrigerator. The semicarbazone and 600 ml. of 10% sulfuric acid was refluxed for a half hour, let stand overnight, and distilled in steam. After working up as already described, distillation at 14 mm. gave:

(A) 2 ml., b. 63–65°, n_D^{20} 1.4803,
(B) 5 ml., b. 65–66°, n_D^{20} 1.4820.
(C) 38 ml., b. 66–66.5°, n_D^{20} 1.4849 (N, Table I)
(D) 3 ml., b. 66.5°, n_D^{20} 1.4862

Anal. Calc'd for $C_7H_{10}O$: C, 76.3; H, 9.15.
Found: (C) C, 75.55; H, 9.6.

Thirty-four g. of this fraction C was distilled twice. The spread of n_D after the first distillation, in which six equal cuts were taken, was 1.4842–1.4858. The four highest boiling cuts were then distilled and four equal cuts (20 ml. in all) were taken. The four all b. 66.7–66.9° and the spread of n_D was 1.4850–1.4857. A fraction, $n_D^{20.2}$ 1.4854, was analyzed. Six weeks later the refractive index had risen to n_D^{20} 1.4892. The solution for ultraviolet spectrum was prepared at this later time. Several other fractions exhibited similar increases in refractive index.

Anal. Calc'd for $C_7H_{10}O$: C, 76.3; H, 9.15.
Found: C, 76.5; H, 9.4.

SUMMARY

1. Slightly impure 1-methyl-1-cyclohexen-6-one has been prepared by two routes from cyclohexanone in 18% yield.

2. The 2,4-dinitrophenylhydrazone of 1-methyl-1-cyclohexen-6-one (a new compound) can be separated from the 2,4-dinitrophenylhydrazone of 1-methyl-1-cyclohexen-3-one by chromatography.

3. Oxidation of 1-methylcyclohexene with selenium dioxide gives 1-methyl-1-cyclohexen-6-one, 1-methyl-1-cyclohexen-3-one, and other products not yet identified.

4. Two compounds isomeric with and closely related to 2-hydroxy-2-methylcyclohexanone have been prepared. One of these m. 173.4–174.4°. The other is a liquid which boils at about 200° under atmospheric pressure.

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY,
MELLON INSTITUTE]

THE ACTION OF SODIUM IODIDE ON SOME ESTERS OF *p*-TOLUENESULFONIC ACID[1]

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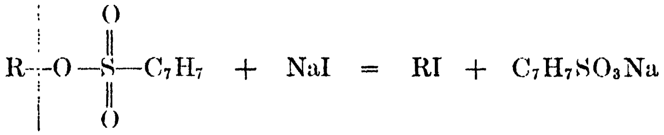
In 1897 it was observed (1) that potassium iodide (in hot alcohol or acetone) converts ethyl *p*-bromobenzenesulfonate to ethyl iodide. Many years later, methyl and ethyl iodides (2, 3) and ethyl α-iodopropionate (4) were prepared in good yield by the action of the same reagent (in boiling water or alcohol) on the corresponding *p*-toluenesulfonates. The method was next applied (5) to the preparation of diisopropylidene-6-iododesoxygalactose from the 6-tosyl derivative, with the improvement of using Finkelstein's reagent (6), namely, sodium iodide dissolved in acetone. Further research has, however, been mainly confined to study of the behavior of tosyl esters of sugar derivatives (7) towards the reagent and it has been found that a primary tosyloxy group is much more reactive than a secondary in such aldo-sugar derivatives as methyl 2,3,4,6-tetratosyl-β-D-glucoside.

The reaction is usually found to proceed as an alkyl-oxygen fission (8) in accordance with the equation:



$$R\,\vdots\!-O-\overset{\overset{\textstyle O}{\|}}{\underset{\underset{\textstyle O}{\|}}{S}}-C_7H_7 \quad + \quad NaI \quad = \quad RI \quad + \quad C_7H_7SO_3Na$$

but a tosyloxy group on the primary alcoholic carbon 1 of certain keto-sugar derivatives is unreactive (9) and if a secondary tosyloxy group is adjacent to a primary tosyloxy group, the formation of an unsaturated substance and free iodine can occur (10). Furthermore, the tosyl esters of naphthol (3), phenol (3, 11), and apocupreine (11) are unreactive, but that of 2,4-dinitrophenol gives rise (11) to *p*-tolyl 2,4-dinitrophenyl sulfone, together with sodium 2,4-dinitrophenate, sodium *p*-toluenesulfonate, and free iodine.

Now, in attempting to prepare certain β-iodoethyloxyquinoline derivatives we decided to investigate the action of sodium iodide (dissolved in acetone) on the corresponding β-*p*-toluenesulfonyloxyethyloxy compounds. We found that the reaction proceeded with great rapidity at *room temperature*, crystallization of sodium *p*-toluenesulfonate commencing after a few minutes. Intrigued by this reactivity, which is so much greater than that displayed by a tosyloxy group on the primary alcoholic carbon of many aldo-sugar derivatives, we decided to study the behavior of a number of simple esters of *p*-toluenesulfonic acid, particularly because, in using such esters as alkylating agents by virtue of their alkyl-oxygen fission, it would be advantageous to know their approximate relative reactivities, in order to facilitate selection of the optimum conditions for performing any particular alkylation. In addition, possession of this knowledge would permit choice of the best procedure for *preparing* the ester to be used as alkylating agent.

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[1] A brief abstract of part of this work was published in *Chem. Eng. News*, **22**, 515 (1944).

Since a high degree of precision appeared unnecessary for our purposes, a method which appeared to us to hold some promise for estimating approximately the ease of replacement of the tosyloxy group was to determine the per cent of sodium *p*-toluenesulfonate formed on treatment with sodium iodide under standard conditions—the action of 2 molar proportions of sodium iodide (10% solution in acetone) at room temperature or during 2 hours at 100° (sealed tube). It is assumed that the resulting solutions or suspensions were not supersaturated with respect to sodium *p*-toluenesulfonate. The question of the mechanism of reaction of the various *p*-toluenesulfonates with sodium iodide will not be considered here.

TABLE I

ACTION OF SODIUM IODIDE IN ACETONE ON ESTERS OF *p*-TOLUENESULFONIC ACID

p-TOLUENESULFONIC ESTER OF	PER CENT YIELD OF SODIUM *p*-TOLUENESULFONATE		
	AT ROOM TEMPERATURE		IN SEALED TUBE AT 100°
	2 hr.	24 hr.	2 hr.
Benzyl alcohol	97	97	
Methanol	96.5	99	
Ethanol	51	99	
n-Propyl alcohol	49.5	98	
β-Ethoxyethanol	14.5	68	
β-Phenoxyethanol	12	67	
β-Benzyloxyethanol	13	69	
Dimethyl carbinol	7.5	53.5	
Diethyl carbinol	23	85	
Di-*n*-propyl carbinol	24		
Ethylene glycol (diester)	16*	73*	
Borneol	0	0	61.5*
l-Menthol	0	1.9*	91*
Cyclohexanol	3*	15*	98*
Thymol	0	0	0

* Free iodine liberated.

The results are given in Table I, from which it may be seen that, with a variety of simple esters of *p*-toluenesulfonic acid, the order of their activities is comparable with that observed by Conant *et al.* (12) for the corresponding organic chlorides treated in a somewhat similar manner. They did not study the behavior of methyl chloride but it has been shown that methyl benzenesulfonate is more reactive than the ethyl ester towards alcohols (13).

The *p*-toluenesulfonates of some phenols, like the simple aryl chlorides (12), do not react. Thus, the thymyl ester is devoid of activity but its hexahydro derivative, the menthyl ester, is more reactive than bornyl and only slightly less reactive than cyclohexyl *p*-toluenesulfonate. Iodine was liberated in the reactions with the last three, presumably owing to the presence of an adjacent labile hydrogen atom and resulting formation of the corresponding unsaturated hydrocarbon. This behavior resembles that of certain vicinal ditosyloxy derivatives (10), a further example of which, ditosyl ethylene glycol, is given in Table I.

The benzyl and methyl esters are very reactive, the ethyl and *n*-propyl esters considerably less so. The activity of the ethyl ester is diminished by introduction of a β-alkoxy group; the ethoxy, phenoxy, and benzyloxy derivatives have about the same reactivity. The esters of the secondary alcohols are less reactive than those of the primary alcohols, and diethyl is more reactive than dimethyl carbinol. Conant (12) remarked on the low reactivity of cyclohexyl chloride; the *p*-toluenesulfonate is similarly of rather low reactivity.

It is well known that the highly reactive ethyl and benzyl *p*-toluenesulfonates cannot be prepared by the reaction of *p*-toluenesulfonyl chloride on the respective alcohol in pyridine at *room temperature*, owing to formation of their pyridinium salts, but can be prepared from these reagents under appropriate conditions (14). We now find that the esters of isopropyl alcohol, menthol, cyclohexanol, and thymol, which prove to be less reactive toward sodium iodide, can be prepared in excellent yield by tosylation at room temperature. Attempts to isolate the *p*-toluenesulfonates of phenyl methyl carbinol and diphenyl carbinol were fruitless, confirming similar work by Kenyon *et al.* (15).

EXPERIMENTAL

Esters of p-toluenesulfonic acid. These were prepared by one or other of the methods previously described (14). *Benzyloxyethyl p-toluenesulfonate* was prepared and purified as described by Clapp and Tipson (16). The following information appears to be new.

Benzyl p-toluenesulfonate was recrystallized from chloroform (2 vol.) plus hexane (10 vol.); m.p. 55–56°. It was kept at room temperature in a vacuum desiccator over phosphorus pentoxide and soda-lime for over three days before decomposition, as evidenced by change in melting point, set in.

Ethyl p-toluenesulfonate was recrystallized from ether (2 vol.) plus pentane (4 vol.); m.p. 33–34°.

n-Propyl p-toluenesulfonate boiled at 106–108° at 0.06 mm. (bath temp., 120°); it was a colorless liquid.

Dimethyl carbinyl p-toluenesulfonate was obtained in 75% yield by the general method (14) (2 hours at 0°); in 60.5% yield after 24 hr. at room temp.; in 90% yield after 2 hr. at room temp. It showed a tendency to decompose on distillation at high vacuum. However, a portion which distilled as a colorless syrup, before decomposition set in, boiled at 107–109° at 0.4 mm. (bath temp. 114–115°). On cooling, it gave a solid mass of colorless crystals, m.p. 20°.

Anal. Calc'd for $C_{10}H_{14}O_3S$: S, 14.97. Found: S, 14.53.

It could be crystallized, without distillation, from ether (2 vol.) plus pentane (12 vol.) by cooling in solid carbon dioxide-chloroform and then keeping overnight in the refrigerator (5°).

Di-n-propyl carbinyl p-toluenesulfonate was obtained as a pale yellow syrup in 60.5% yield (24 hr. at room temp.). It was freed from traces of solvent under a high vacuum at room temperature, since it decomposed on attempted distillation.

Anal. Calc'd for $C_{14}H_{22}O_3S$: S, 11.86. Found: S, 11.47, 11.35.

l-Menthyl, cyclohexyl, and thymyl p-toluenesulfonates were prepared as described for the bornyl ester (14) in yields of 96.5%, 98.5%, and 100%, respectively.

l-Menthyl ester. The crude, colorless crystals (m.p. 91–93°) were recrystallized from hexane (5 vol.), m.p. 93–95°. Again so recrystallized it had m.p. 94–95°, $[\alpha]_D^{24}$ −68.2° (in chloroform). Hilditch (17) gave m.p. 97°, $[\alpha]_D^{20}$ −66.8° (in chloroform).

Cyclohexyl ester. The crude, colorless crystals (m.p. 42–43°) were recrystallized twice from ether (1 vol.) plus pentane (2 vol.), m.p. 45–46°. Hückel (18) gave m.p. 44–45°.

Thymyl ester (20.2 g.) was recrystallized by dissolving in 1.5 volumes of dry ether at room temperature, adding 1.5 volumes of pentane, filtering, and cooling, to give a first crop of 10.6 g. of colorless crystals, m.p. 69–70°. On recrystallization from 3 volumes of ether plus 3 volumes of pentane, it had m.p. 71–72°.

Anal. Calc'd for $C_{17}H_{20}O_3S$: S, 10.54. Found: S, 10.60.

Attempted preparation of diphenyl carbinyl p-toluenesulfonate. (A) *In pyridine during 2 hours at 0° or 24 hours at 25°.* No crystals of pyridine hydrochloride formed. The original weight of unchanged, crystalline diphenyl carbinol was recovered, m.p. 65–66°. Recrystallized from chloroform (1 vol.) plus hexane (10 vol.) it had m.p. 68° and was devoid of sulfur.

(B) *In boiling ether containing dimethylaniline (19).* No apparent reaction took place on adding 1 equivalent of dimethylaniline to the ether solution of reactants and boiling for 5 hours.

(C) *2 Hours in boiling benzene.* A solution of diphenyl carbinol (m p. 68°; 5 g.) and *p*-toluenesulfonyl chloride (5.7 g.) in 35 cc. of benzene was boiled under reflux ("Drierite" tube) for 2 hours The yellow solution (containing a trace of a liquid layer) was washed with distilled water, the water becoming strongly acid to Congo Red, and then successively with aqueous sodium bicarbonate solution and water until neutral. It was dried with sodium sulfate and evaporated to dryness, giving 10.7 g. of pale yellow crystals, partly melting at 53–55° and completely molten at 80°. In order to ensure decomposition of any *p*-toluenesulfonyl chloride, it was dissolved in 50 cc. of pyridine and 50 cc. of water was added. On cooling in ice, a yellow oil separated and crystallized. The colorless crystals were filtered off, washed with water until free from pyridine, and dried; wt. 4.4 g., m.p. 106–108°.

It was recrystallized from 10 volumes of absolute ethanol, giving 4.3 g. of crystals, m.p. 110°, which were devoid of chlorine or sulfur.

Anal. Calc'd for $C_{26}H_{22}O$: C, 89.10, H, 6.33.

Found: C, 88.51, H, 6.32.

These results indicate a yield of over 90% of *s*-tetraphenyldimethyl ether [for which Ward (20) gave m.p. 110°].

On repeating the preparation, with boiling for only 30 minutes, a quantitative yield of crude product, m.p. 106–108°, was obtained.

Attempted preparation of phenyl methyl carbinyl p-toluenesulfonate. No apparent reaction occurred between tosyl chloride and phenyl methyl carbinol in pyridine during 2 hours either at 0° or 65–70°.

Action of sodium iodide on p-toluenesulfonates. Anhydrous sodium iodide (0.5 g.) was weighed into a test tube, and one-half the theoretical weight of ester and 5 cc. of acetone were added. The tube was tightly stoppered and gently swirled at room temperature until the reactants had dissolved completely. The time for the first appearance of crystals was noted and, after the elapse of a suitable period of time, the sodium *p*-toluenesulfonate was filtered off, washed with acetone, dried, and weighed. It was then treated with water, to make sure that it contained no water-insoluble material, and the solution was tested for inorganic iodide (which was invariably absent).

At room temperature, crystals appeared instantaneously with the benzyl and methyl esters; in less than 5 minutes with the ethyl and *n*-propyl esters; and in 10 to 20 minutes with the other reactive esters shown in Table I.

In those cases where reaction did not proceed appreciably at room temperature, a solution of the same composition was sealed in a tube which was then heated in a boiling water-bath during two hours. The tube was cooled and the sodium *p*-toluenesulfonate isolated as above.

SUMMARY

The reaction of certain esters of *p*-toluenesulfonic acid with sodium iodide dissolved in acetone has been studied. Their reactivities are found to be in the same relative order as those of the corresponding organic chlorides towards the same reagent.

The tosyl esters of isopropyl alcohol and thymol have been obtained in crystalline condition. The less reactive esters studied may be prepared in good yield in the presence of pyridine at room temperature.

PITTSBURGH 13, PA.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

BIOTIN. I. 2-ALKYLTHIOPHANE-3,4-DICARBOXYLIC ACIDS

B. R. BAKER, MERLE V. QUERRY, S. R. SAFIR, AND SEYMOUR BERNSTEIN

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Interest in the little known field of functional derivatives of thiophane has been given incentive by the elucidation of the structure of biotin, 2-(δ-carboxybutyl)-5-ketoimidazolido[4,5,c]thiophane, by duVigneaud and his collaborators (1a). In the course of the structure proof of biotin, the diethyl ester of thiophane-3,4-dicarboxylic acid (1b) was synthesized and converted to derivatives of 3,4-diaminothiophane by the Curtius degradation.[1]

In this communication is described the preparation of 2-propyl- and 2-(γ-phenoxypropyl)thiophane-3,4-dicarboxylic acids (XI) by general methods, the separation of some of the isomers, and their behavior in the Curtius degradation.

When butylideneacetonitrile (IIa) was condensed with ethyl thioglycolate (I) in benzene in the presence of sodium ethoxide, the sulfhydryl group added to the conjugated double bond and the intermediate thio ether underwent a Dieckmann cyclization to form 2-propyl-3-cyano-4-ketothiophane (IVa). This nitrile, characterized by its crystalline semicarbazone, was converted to 2-propyl-3-carbethoxy-4-ketothiophane (Va) *via* the imino ether. However, the keto ester (Va) was more conveniently prepared by the condensation of ethyl thioglycolate and ethyl 2-hexenoate (IIIa) in boiling benzene in the presence of sodium ethoxide. In this reaction either 2-propyl-3-carbethoxy-4-ketothiophane (Va) or 2-propyl-4-keto-5-carbethoxythiophane (VIa) or a mixture of the two may be formed depending upon which way the intermediate thio ester cyclizes. Identity of the semicarbazones of the keto esters, Va, prepared from either the nitrile, IVa, or ethyl 2-hexenoate (IIIa) showed that ring closure had taken place mainly to the desired 2-propyl-3-carbethoxy-4-ketothiophane (Va).[2]

The keto esters, Va and Vb, were further characterized by treatment with dilute sulfuric acid, which readily decarbalkoxylated them to the 2-alkyl-4-thiophanones, VII.

By the action of liquid hydrogen cyanide on 2-propyl-3-carbethoxy-4-ketothiophane (Va) a cyanohydrin, VIIIa, was formed in excellent yield and was smoothly hydrolyzed with hydrochloric acid to a non-crystalline mixture of isomeric 2-propyl-4-hydroxythiophane-3,4-dicarboxylic acids (IXa). Distillation *in vacuo* from either 85% phosphoric acid or potassium bisulfate effected dehydration to 2-propyldihydrothiophene-3,4-dicarboxylic acid (Xa) mainly in the form of its anhydride. The double bond, the position of which was unknown, was readily reduced with sodium amalgam in dilute alkali at 70–80° to a mixture of isomeric 2-propylthiophane-3,4-dicarboxylic acids (XIa). One

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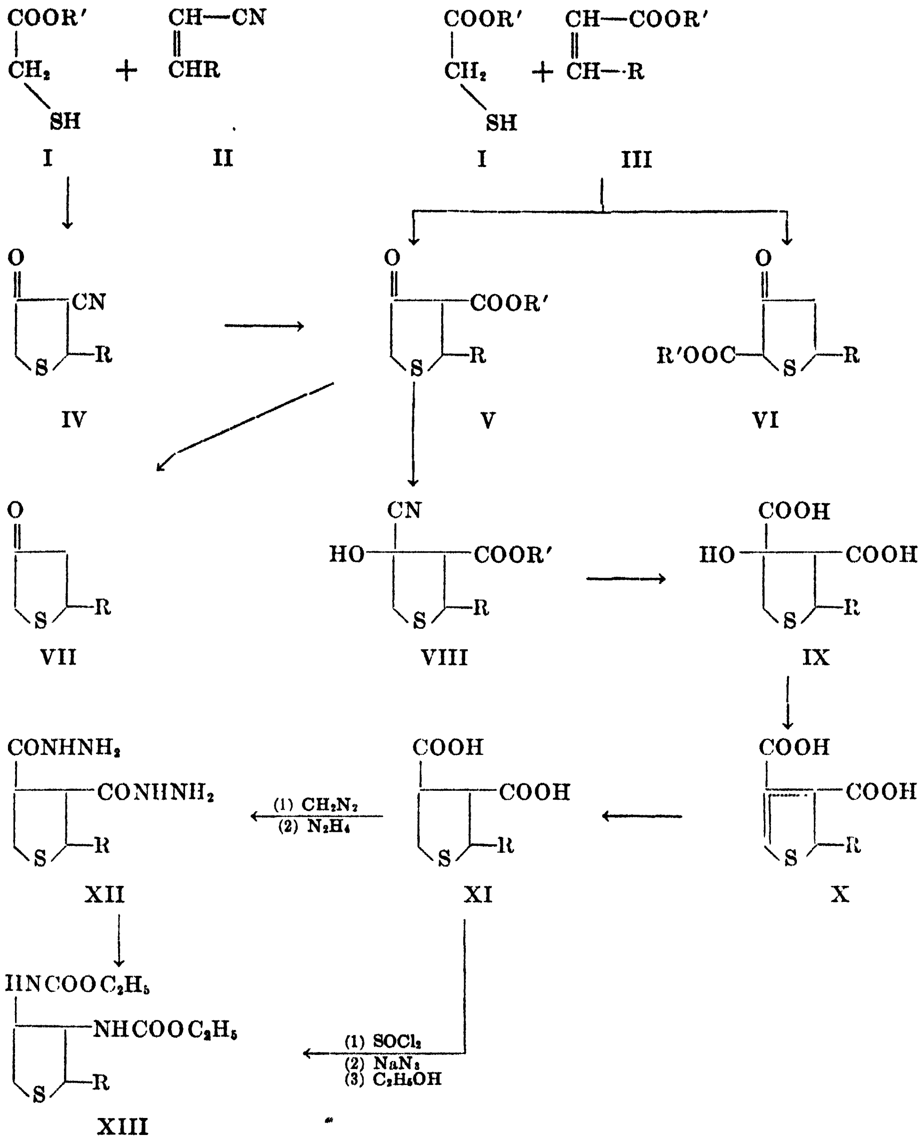
[1] A different isomer was obtained in a second synthesis (2). The stereochemical configuration of these two forms is now described in an accompanying communication.

[2] After this work was completed Woodward and Eastman (3) showed that Dieckmann cyclization of methyl β-(carbomethoxymethylthio)propionate at high temperature gave a keto ester, V (R=H), while low temperature favored the formation of the keto ester, VI (R = H).



a series R = *n*-C_3H_7-, R' = C_2H_5-
b series R = C_6H_5O-$(CH_2)_3$-, R' = CH_3-

crystalline isomer, m.p. 156–157°, was easily isolated, due to its insolubility in benzene.

The crystalline isomer was shown to have its carboxyl groups related by a *trans* configuration as (a) it was stable to heat at 250°; (b) it gave a diacid chloride with thionyl chloride; (c) it formed a mixed anhydride when treated with acetyl chloride and the same acid was regenerated on hydrolysis; (d) it was converted with boiling propionic anhydride to a mixture of isomeric *cis* anhydrides from which a crystalline *cis* diacid, m.p. 130–131°, could be isolated. The carboxyl groups of the latter have a *cis* configuration as (a) acetyl chloride or thionyl chloride gave an inner anhydride which regenerated the same acid on treatment with water; (b) it evolved water at 150° to form an anhydride; (c) it formed a cyclic imide. Thus, two of the possible four racemic modifications of 2-propylthiophane-3,4-dicarboxylic acid (XIa) have been characterized, one *cis* and one *trans*.

The preparation of 2-(γ-phenoxypropyl)thiophane-3,4-carboxylic acid (XIb) followed the same reactions except that dehydration of the hydroxy acid, IXb, was accomplished by means of boiling acetic anhydride. Again a *trans* diacid, m.p. 183°, was readily separated and was convertible to the *cis* anhydrides with boiling propionic anhydride. One of the *cis* anhydrides, m.p. 105°, was isolated and hydrolyzed to a *cis* diacid, m.p. 158°. The *cis* and *trans* configurations were established in the same manner as for the 2-propylthiophane-3,4-dicarboxylic acids (XIa).

2-(γ-Phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid (XIb) was prepared by a second method. γ-Phenoxypropylmalonic acid (XIV) on chlorination with sulfuryl chloride followed by decarboxylation gave a mixture of 5-phenoxyvaleric acid, 5-chlorophenoxyvaleric acid, 2-chloro-5-phenoxyvaleric acid (XVI), and 2-chloro-5-chlorophenoxyvaleric acid. The mixture was treated with sodium hydrosulfide, then esterified. Cold alkaline extraction of an ethereal solution of the esters gave on acidification a mixture of methyl 2-mercapto-5-phenoxyvalerate (XVIII) and methyl 2-mercapto-5-chlorophenoxyvalerate, which were separated by fractional distillation, in yields of 14% and 8% respectively based on the original malonic acid, XIV.

Condensation of the methyl 2-mercapto-5-phenoxyvalerate (XVIII) with methyl acrylate in the presence of piperidine followed by Dieckmann cyclization with sodium methoxide in ether proceeded smoothly to 2-(γ-phenoxypropyl)-3-keto-4-carbomethoxythiophane (XIX). In this case the Dieckmann reaction can take place only as indicated, as formation of the isomeric 2-(γ-phenoxypropyl)-2-carbomethoxy-3-ketothiophane would involve the elimination of methanol between a carbomethoxy group and a tertiary hydrogen, which takes place only with difficulty (4).

The keto ester, XIX,[3] was converted to 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid by the same series of reactions used for the isomeric 2-(γ-phenoxypropyl)-3-carbomethoxy-4-ketothiophane (Vb). The crystalline *trans* acids obtained by both methods were identical, thus offering additional proof of the direction of ring closure in the preparation of the keto ester, Vb. The yield of crystalline *trans* diacid, m.p. 183°, obtained on sodium amalgam reduction of XXII, was 29%. The isomers in the filtrate were esterified, treated with sodium methoxide to invert *cis* isomers to *trans* and then hydrolyzed. Another 20% of the same crystalline *trans* acid was obtained. The filtrate from this material presumably contained a second *trans* isomer which did not crystallize. It was boiled with propionic anhydride in order to invert it back to the *cis* isomers, then esterified and reinverted back to the *trans* isomers by treatment

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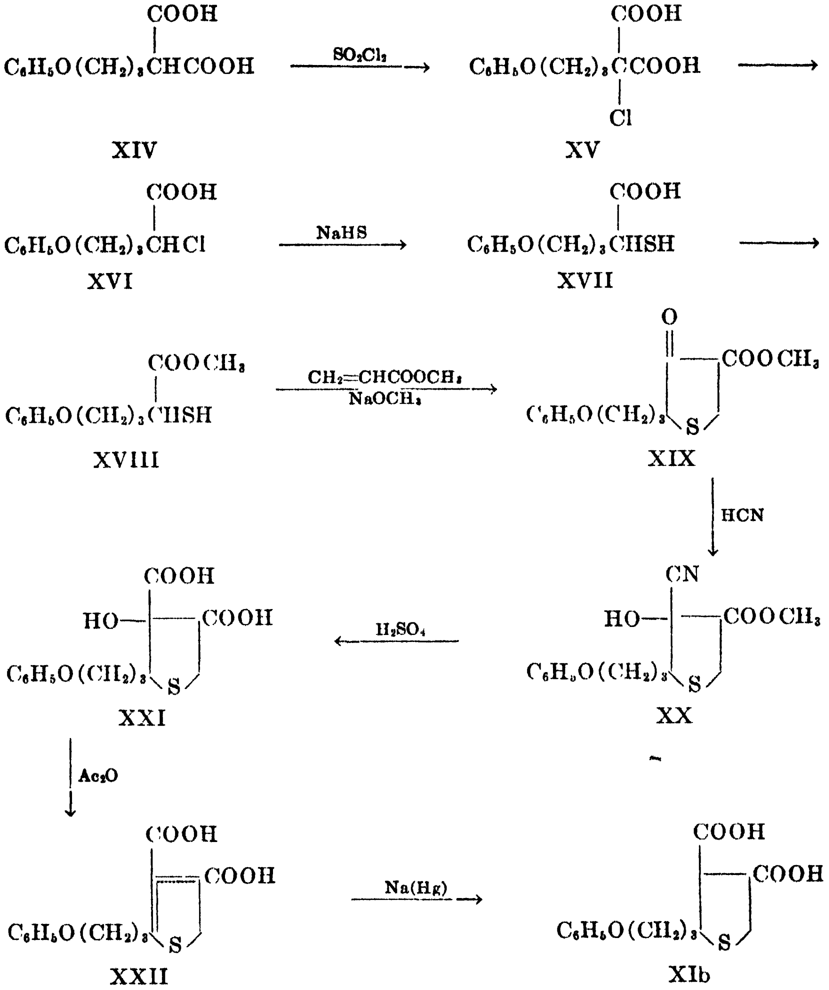
[3] After this work was completed Cheney and Piening (20) published a superior method for the preparation of the corresponding keto ethyl ester.



with sodium methoxide. In this way an additional 7%, a total of 56%, of the crystalline *trans* isomer was obtained.[4]

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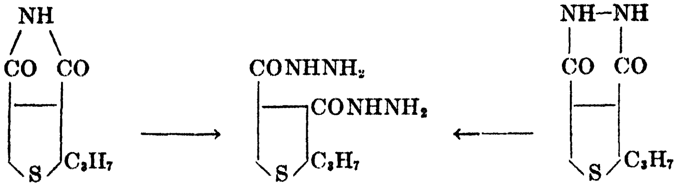
[4] Since completion of this work, Grüssner, Bourguin, and Schnider (21) have described the synthesis of the dimethyl ester of 2-(δ-methoxybutyl)thiophane-3,4-dicarboxylic acid by a somewhat similar method. However, they did not isolate and characterize any of the isomers of the diacid.

The *trans* dicarboxylic acids, XI, were converted *via* the methyl esters to the *trans* dihydrazides, XII, which were in turn degraded by the Curtius method to the *trans*[5] diurethans. The 2-(γ-phenoxypropyl)-3,4-*trans*-dicarbethoxylaminothiophane (XIIIb) was prepared more easily and in better yield by treating the diacid chloride of the *trans* dicarboxylic acid, XI, with sodium azide in dilute acetone (6). However, when the esters of 2-propyl- or 2-(γ-phenoxypropyl)-thiophane-3,4-*cis*-dicarboxylic acids were treated with hydrazine under a variety of conditions, no *cis* dihydrazides[6] could be isolated, but inversion to the *trans* dihydrazides, XII, took place. Similarly when the imide (XXIII) or cyclic hydrazide (XXIV) of 2-propylthiophane-3,4-*cis*-dicarboxylic acid was treated with hydrazine, the *trans* dihydrazide, XIIa, was formed. Apparently hydrazine is sufficiently alkaline to cause rearrangement of a *cis* diester or *cis* dihydrazide to the more stable *trans* configuration by enolization of the carbonyl groups in the same manner as sodium methoxide.



cis XXIII — trans XIIa — cis XXIV

In view of these results it is highly probable that the 3,4-diaminothiophane of duVigneaud (1b) has a *trans* configuration. The diacid chloride-sodium azide procedure could not be applied to the *cis* diacids, as they were, as in the case of succinic acid (8), converted to the anhydrides on treatment with thionyl chloride or oxalyl chloride. The method used for preparing succinyl chloride by long treatment of the acid with phosphorus pentachloride (9) was unsuccessful in the thiophane series as only dark tars were formed.

The Schmidt (10) hydrazoic acid degradation of either the *cis* or *trans* diacids failed to take place and no nitrogen was evolved. The thio ether linkage β to the carboxyl groups in the thiophane series may have an inhibitory effect on the course of the reaction.

It had been planned to hydrolyze simultaneously the urethan and phenoxy groups of 2-(γ-phenoxypropyl)-3,4-*trans*-dicarbethoxyaminothiophane (XIIIb) with 48% hydrobromic acid to form 2-(γ-bromopropyl)-3,4-*trans*-diaminothiophane dihydrobromide (XXV). By blocking the amine groups followed by treatment with malonic ester, the side chain would have been completed to valeric acid.

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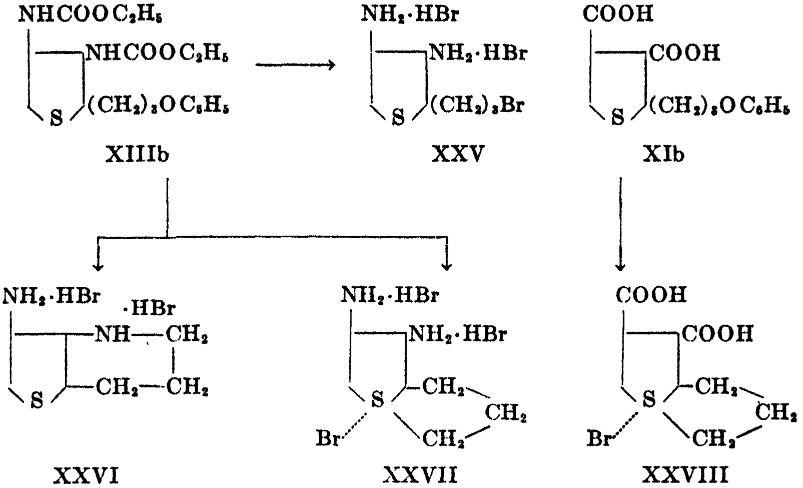
[5] Jones and Wallis (5) have demonstrated that the Curtius rearrangement takes place with retention of configuration. See also reference 7.

[6] Buchman, Reims, Skei, and Schlatter (7) observed that in the cyclobutane series either a *cis* or *trans* dihydrazide of the 1,2-dicarboxylic acid could be prepared from the corresponding *cis* or *trans* diester.



Unfortunately, the preparation of 2-bromopropylthiophanes by this method was unsuccessful as ring closure to a sulfonium bromide took place readily. The ease with which this type of ring closure takes place was demonstrated by hydrolysis of 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid (XIb). When the acid was refluxed with 48% hydrobromic acid for *only twenty minutes* a 59% yield of the water-soluble 1,2-trimethylene-3,4-dicarboxythiophanium bromide (XXVIII)[7] was obtained.

The hydrolysis of the phenoxy urethan, XIIIb, appeared to give a mixture of 1,2-trimethylene-3,4-*trans*-diaminothiophanium bromide dihydrobromide (XXVII) and 3-aminopiperidino[3,2,b]thiophane dihydrobromide (XXVI). The latter could be separated as its water-insoluble dibenzoate and the presence of the former was assumed by analogy with the hydrolysis of XIb as well as by the analytical data. The presence of the bromopropyldiamine, XXV, in the mixture could not be detected.

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EXPERIMENTAL

Butylideneacetonitrile (II). A mixture of 75 g. of butylidenecyanoacetic acid (11), 75 cc. of quinoline, and 0.8 g. of copper oxide was heated in a 250 cc. modified Claisen flask at 125–140° (bath) for twenty-five minutes, when the evolution of carbon dioxide had practically ceased. The product was distilled out of the reaction mixture at 15 mm. until the vapors reached 110°. Redistillation gave in four runs 23.5–24.3 g. (46–48%) of a water-white liquid, b.p. 57–59° (12 mm.).

Letch and Linstead (11) decarboxylated this acid by heating its mixture with sand, and reported that the yield varied widely and never exceeded 40%. They record the boiling point 57–58° (11 mm.).

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[7] Bennet and Hock (22) have observed a similar type of ring closure on hydrobromic acid hydrolysis of bis-(δ-benzyloxybutyl) sulfide. The product was 1-(δ-hydroxybutyl)-thiophanium bromide and no bis-(δ-bromobutyl) sulfide could be isolated.

Ethyl thioglycolate. A mixture of 150 g. of thioglycolic acid, 200 cc. of absolute ethanol, 300 cc. of benzene, and 20 cc. of concentrated sulfuric acid was refluxed for sixteen hours under a Soxhlet apparatus containing about 90 g. of anhydrous magnesium sulfate in the thimble. The cooled mixture was washed twice with water, solvent removed through a Vigreux column, and the residue distilled; colorless liquid, b.p. 63° (20 mm.); yield, 174 g. (89%). If water is not continuously removed, as in the ordinary esterification, the yield is about 60%.

The methyl ester may be prepared similarly using methanol and chloroform; yield, 77–82%.

This method (12) is used routinely for all esterifications of this type and has been found to give invariably higher yields than can be obtained without continuous drying.

Methyl 2-hexenoate. 2-Hexenoic acid was prepared from *n*-butyraldehyde and malonic acid according to Goldberg and Linstead (13), except that a 25% excess of aldehyde was employed and the reaction was allowed to proceed for seventeen hours at room temperature; yield, 76% of product, m.p. 32°.

From 278 g. of 2-hexenoic acid, 300 cc. of methanol, 300 cc. of chloroform, and 30 cc. of concentrated sulfuric acid, using 90 g. of anhydrous magnesium sulfate for continuous drying as described above, was obtained 305 g. (98%) of the ester, b.p. 56–58° (13 mm.).

The ethyl ester was prepared in the same manner using ethanol and benzene, b.p. 72–73° (15 mm.); yield, 94%.

The esterification reaction of 2-hexenoic acid has been found by Thomas and Sudborough (14) to be sensitive to water and they have shown that at equilibrium only 15% of the methyl ester is formed. The only esterification of this acid reported in the literature is that of Kon, Linstead, and MacLennan (15) who treated the silver salt with ethyl iodide. They record the b.p. 80° (22 mm.).

Methyl 6-phenoxy-2-hexenoate (IIIb). From 46 g. of 6-phenoxy-2-hexenoic acid (23), 5 cc. of concentrated sulfuric acid, 100 cc. of methanol, and 100 cc. of chloroform was obtained 42 g. (86%) of the ester by the continuous drying procedure; b.p. 135–138° (1 mm).

Anal. Calc'd for $C_{13}H_{16}O_3$: C, 70.8; H, 7.3.
Found: C, 70.4; H, 6.8.

2-Propyl-3-cyano-4-ketothiophane (IVa). To the dry sodium ethoxide from 8.3 g. of sodium and 150 cc. of absolute ethanol, obtained by evaporating the solution to dryness *in vacuo*, was added in a nitrogen atmosphere a solution of 42.5 g. of ethyl thioglycolate in 60 cc. of benzene. After most of the sodium ethylate had dissolved, a solution of 37.2 g. of butylideneacetonitrile in 30 cc. of benzene was added. The solution was refluxed for one hour on the steam-bath, during which the sodium salt of the product separated. The cooled mixture was extracted with ice-water, the extracts immediately acidified, and the oil which separated was extracted with benzene. Distillation gave 31 g. (52%) of a yellow oil, b.p. 125–127° (1 mm.), n_D^{20} 1.5118.

Anal. Calc'd for $C_8H_{11}NOS$: C, 56.7; H, 6.5; N, 8.3.
Found: C, 56.4; H. 6.3; N, 7.8.

The semicarbazone formed white crystals from dilute alcohol, m.p. 175–176°.

Anal. Calc'd for $C_9H_{14}N_4OS$: C, 47.8; H, 6.2; N, 24.8.
Found: C, 48.1; H, 6.1; N, 25.2.

2-Propyl-3-carbethoxy-4-ketothiophane (Va). *A.* A mixture of 15 g. of 2-propyl-3-cyano-4-ketothiophane (IVa) in 7 cc. of absolute alcohol was treated with dry hydrogen chloride until 3.3 g. had been absorbed. After two days in a stoppered flask, the mixture was diluted with water and benzene and stirred for twenty hours. The separated benzene layer was extracted twice with iced 5% sodium hydroxide and the extracts immediately acidified with acetic acid. The oily layer was taken up in benzene, then distilled, b.p. 108–111° (1 mm.), n_D^{20} 1.4927; yield, 9 g. (47%).

Anal. Calc'd for $C_{10}H_{16}O_3S$: C, 55.6; H, 7.4.
Found: C, 55.4; H, 6.8.

The semicarbazone slowly formed in dilute alcohol and was purified by recrystallization from the same solvents, white crystals, m.p. 163–165°.

Anal. Calc'd for $C_{11}H_{19}N_3O_3S$: C, 48.3; H, 7.0; N, 15.4.
Found: C, 48.3; H, 6.8; N, 15.0.

B. This ester was more conveniently prepared by refluxing for three hours a solution of sodium ethoxide (from 23 g. of sodium), 109 g. of ethyl thioglycolate, and 132 g. of ethyl 2-hexenoate in 300 cc. of benzene according to the procedure described for 2-propyl-3-cyano-4-ketothiophane (IVa); light yellow oil, b.p. 110–113° (1 mm.); yield, 130 g. (66%). The semicarbazone formed white crystals from dilute alcohol, m.p. 162–164°, alone or when mixed with semicarbazone described in part *A*.

The corresponding methyl ester was prepared analogously using the sodium methoxide from 57 g. of sodium, 227 g. of methyl thioglycolate and 297 g. of methyl 2-hexenoate; yield, 223 g. (52%) of oil, b.p. 112–114° (3 mm.), n_D^{25} 1.4963.

Anal. Calc'd for $C_9H_{14}O_3S$: C, 53.4; H, 7.0.
Found: C, 53.2; H, 6.6.

The semicarbazone melted at 156–158°.

2-(γ-Phenoxypropyl)-3-carbomethoxy-4-ketothiophane (*Vb*). From 23 g. of sodium methoxide (Mathieson Alkali Works), 32 g. of methyl thioglycolate, 63.4 g. of methyl 6-phenoxy-2-hexenoate (IIIb), and 150 cc. of benzene was obtained 60.5 g. (72%) of a non-distilled alkali-soluble fraction in the same manner as described for the corresponding propyl compound. This was sufficiently pure for the next step, but could be further purified by evaporative distillation at a pressure of 1 micron and bath temperature of 110° as a light yellow oil with 90% recovery.

Anal. Calc'd for $C_{15}H_{18}O_4S$: C, 61.3; H, 6.2.
Found: C, 61.9; H, 6.0.

The semicarbazone formed white crystals from methanol, m.p. 143–144.5°.

Anal. Calc'd for $C_{16}H_{21}N_3O_4$: C, 54.7; H, 6.0; N, 11.9.
Found: C, 54.9; H, 5 8; N, 11 5, 11.5.

The keto ester could not be distilled at 1 mm. as it decomposed to give 2-(γ-phenoxypropyl)-4-ketothiophane (VIIb) and a large amount of tar.

2-Propyl-4-ketothiophane (*VIIa*). A mixture of 33.5 g. of 2-propyl-3-carbethoxy-4-ketothiophane (Va), 40 cc. of acetic acid, 21 cc. of concentrated sulfuric acid, and 150 cc. of water was refluxed for six hours. The cooled mixture was extracted with benzene and the extract washed with 10% sodium hydroxide. Solvent was removed through a Vigreux column and the residue distilled; colorless liquid, b.p. 98° (12 mm.); yield, 17.8 g. (80%).

Anal. Calc'd for $C_7H_{12}OS$: C, 58.3; H, 8.3.
Found: C, 58.5; H, 8.0.

The semicarbazone crystallized from dilute alcohol in the form of white plates, m.p. 161–162°.

Anal. Calc'd for $C_8H_{15}N_3OS$: C, 47.7; H, 7.5; N, 20.9.
Found: C, 47.7; H, 6.9; N, 20.9.

2-(γ-Phenoxypropyl)-4-ketothiophane (*VIIb*). This keto ester was prepared from 2-(γ-phenoxypropyl)-3-carbomethoxy-4-ketothiophane in the same manner as described for the ketone above. The product was purified by distillation at 1 mm. in a two-bulbed flask followed by recrystallization from methanol or petroleum ether (b.p. 30–60°); white crystals, m.p. 59–61°.

Anal. Calc'd for $C_{13}H_{16}O_2S$: C, 66.2; H, 6.8.
Found: C, 65.9; H, 6.3.

The semicarbazone formed white crystals from alcohol, m.p. 159–160°.

Anal. Calc'd for $C_{14}H_{19}N_3O_2S$: C, 57.3; H, 6.5; N, 14.3.
Found: C, 57.1; H, 6.9; N, 14.0.

2-Propyl-3-carbethoxy-4-hydroxy-4-cyanothiophane (*VIIIa*). It was not necessary to use anhydrous hydrogen cyanide in this reaction and therefore its method of preparation could be greatly simplified. Fifty per cent by volume sulfuric acid was dropped on potassium cyanide crystals, the vapors led to a vertical tube cooled in an ice-bath and the liquid caught in an ice-cooled graduated cylinder; yield about 70%.

To 30 cc. of liquid hydrogen cyanide and 0.3 cc. of 50% potassium hydroxide cooled in an ice-bath was added 100 g. of 2-propyl-3-carbethoxy-4-ketothiophane (Va) in portions, maintaining the temperature at 10–15°. After fifteen hours at 0° the mixture was acidified with 0.6 cc. of 85% phosphoric acid. The excess hydrogen cyanide was removed *in vacuo* through an aqueous alkali trap and the residue distilled; yellow oil, b.p. 142–145° (1 mm.), n_D^{25} 1.4911; yield, 107 g. (95%).

Anal. Calc'd for $C_{11}H_{17}NO_3S$: C, 54.3; H, 7.0; N, 5.8.
Found: C, 54.5; H, 6.6; N, 5.7.

The methyl ester was prepared in the same manner in 94% yield, b.p. 139–142° (1 mm.), n_D^{25} 1.4968.

Anal. Calc'd for $C_{10}H_{15}NO_3S$: C, 52 3; H, 6.2; N, 6.1.
Found: C, 52.7; H, 6.3; N, 6.2.

If the excess acid is washed out of the cyanohydrin, then it dissociates back into its starting components on distillation.

2-Propyl-4-hydroxythiophane-3,4-dicarboxylic acid (*IXa*). A mixture of 50 g. of 2-propyl-3-carbethoxy-4-hydroxy-4-cyanothiophane (VIIIa), 100 cc. of acetic acid, and 250 cc. of concentrated hydrochloric acid was refluxed for twenty hours. The solution was diluted to 1 liter with water and clarified with Norit. After saturation with salt, the solution was extracted with three 250-cc. portions of ethyl acetate, the extracts dried with magnesium sulfate, then evaporated to dryness *in vacuo*. The product, a mixture of stereoisomers, was a gum; yield, 46.6 g. (97%).

Anal. Calc'd for $C_9H_{14}O_5S$: C, 46.2; H, 6.0.
Found: C, 46.6; H, 5.4.

In later runs it was found advantageous to hydrolyze the crude cyanohydrin, VIIa, prior to distillation. The over-all yield from the keto ester was 90%.

Anal. Found: C, 46.0; H, 5.5.

The dimethyl ester was formed in 74% yield by the usual continuous drying method with methanol, chloroform, sulfuric acid, and anhydrous magnesium sulfate; light yellow oil, b.p. 135–138° (1 mm.), n_D^{23} 1.4917.

Anal. Calc'd for $C_{11}H_{18}O_5S$: C, 50.3; H, 6.9.
Found: C, 50.3; H, 6.3.

2-Propyl-3-carbomethoxy-4-cyanodihydrothiophene. To a solution of 6 g. of 2-propyl-3-carbomethoxy-4-hydroxy-4-cyanothiophane in 10 cc. of dry pyridine was added 4.7 cc. of phosphorus oxychloride. The temperature was maintained at 38–43° by occasional cooling until the temperature began to drop. After twenty hours at room temperature, the mixture was poured on iced hydrochloric acid and the oil extracted with benzene. The extract was washed with dilute hydrochloric acid and solvent removed. The residue distilled as a light yellow oil, b.p. 128–132° (1 mm.), n_D^{23} 1.5225; yield, 3.9 g. (71%).

Anal. Calc'd for $C_{10}H_{13}NO_2S$: C, 56.8; H, 6.2; N, 6.6.
Found: C, 56.7; H, 5.6; N, 6.5.

The use of thionyl chloride in this dehydration (16) gave a product contaminated with much free sulfur and difficulty with emulsions was encountered in the work-up. The yield was about the same.

2-(γ-Phenoxypropyl)-4-hydroxythiophane-3,4-dicarboxylic acid (*IXb*). To a mixture of 60.5 g. of 2-(γ-phenoxypropyl)-3-carbomethoxy-4-ketothiophane (Vb) and 35 cc. of liquid hydrogen cyanide cooled in an ice-bath was added 0.5 cc. of 50% potassium hydroxide. The mixture soon became homogeneous on swirling. After twenty-three hours at 0–5°, the mixture was acidified with 2 cc. of 85% phosphoric acid and the excess hydrogen cyanide removed *in vacuo*. The residual cyanohydrin was refluxed with 180 cc. of acetic acid, 450 cc. of water, and 63 cc. of concentrated sulfuric acid for twelve hours, then diluted to 2 l. with water. The oil was taken up in ethyl acetate and extracted with aqueous sodium bicarbonate solution. The ethyl acetate layer was washed with water and evaporated. The residue consisted of 10.5 g. (22%) of crude 2-(γ-phenoxypropyl)-4-ketothiophane (VIIb), which was purified as previously described.

The sodium bicarbonate solution of acidic material was acidified, the oil extracted with ethyl acetate, and the latter washed twice with water containing a little salt.[8] Evaporation of the ethyl acetate *in vacuo* gave 40 g. (60%) of product as a gummy mixture of stereoisomers which was used in the next step without further purification.

One of the isomers crystallized when a benzene solution of the mixture was allowed to stand. It was purified by recrystallization from ethylene dichloride-acetone, then dilute acetic acid, white crystals, m.p. 200–202° dec.

Anal. Calc'd for $C_{15}H_{18}O_6S$: C, 55.2; H, 5.5.
Found: C, 55.2; H, 5.1.

When the cyanohydrin, VIIIb, was hydrolyzed with hydrochloric acid in acetic acid in the same manner as described for 2-propyl-3-carbethoxy-4-hydroxy-4-cyanothiophane (VIIIa), no product could be isolated except small amounts of phenol.

2-Propyldihydrothiophene-3,4-dicarboxylic acid (Xa) and anhydride. A mixture of 19 g. of 2-propyl-4-hydroxythiophane-3,4-dicarboxylic acid (IXa) and 0.1 cc. of 85% phosphoric acid was distilled at 2–8 mm. and a bath temperature of 190–210°. Redistillation gave 11.1 g. of an oil, b.p. 125–145° (1 mm.). Analyses indicated a mixture of the acid and anhydride. About the same results were obtained when 1 g of potassium bisulfate was substituted for the phosphoric acid.

A mixture of 9.5 g. of the above distillate, 2 cc. of concentrated sulfuric acid, 40 cc. of methanol, and 60 cc. of chloroform was refluxed overnight with continuous drying in the usual manner. The 2-propyl-3,4-dicarbomethoxydihydrothiophene was obtained as an oil, b.p. 123–125° (1 mm.), n_D^{23} 1.5018; yield, 8.4 g. (72%).

Anal. Calc'd for $C_{11}H_{16}O_4S$: C, 54.2; H, 6.6.
Found: C, 54.2; H, 5.8.

A crystalline acid, m.p. 150–152°, was obtained by treatment of the pyrolysis distillate with water followed by crystallization from benzene.

Anal. Calc'd for $C_9H_{12}O_4S$: C, 50.0; H, 5.6.
Found: C, 50.4; H, 5.4.

γ-Phenoxypropylmalonic acid (XIV). This acid, prepared by methods described in the literature (17), has been reported as melting indefinitely between 70° and 100°. This has been found to be due to water of crystallization. The anhydrous material can be obtained by refluxing its solution in benzene, with or without the addition of ethyl acetate to aid solubility, under a constant water separator until no more water is removed. On cooling, the solution deposits crystals of the anhydrous acid, m.p. 113–114° (20).

Anal. Calc'd for $C_{12}H_{14}O_5$: C, 60.4; H, 5.9.
Found: C, 60.2; H, 5.5.

Methyl 2-mercapto-5-phenoxyvalerate (XVIII). To a refluxing solution of 160 g. of anhydrous γ-phenoxypropylmalonic acid (XIV) in 640 cc. of chloroform was added dropwise over a period of twenty minutes 57 cc. of sulfuryl chloride. After being refluxed for ninety minutes more, the solution was evaporated to dryness *in vacuo*. The residue was heated with 1.6 g. of copper oxide at 145–160° until carbon dioxide evolution was complete which required twenty-five minutes.

The cooled residue was dissolved in 400 cc. of water containing 37 g. of anhydrous sodium carbonate and added to a solution of 54 g. of sodium hydroxide in 280 cc. of water saturated with hydrogen sulfide. After being heated on the steam-bath for ninety minutes, the solution was poured into a mixture of ice and 200 cc. of concentrated hydrochloric acid. The viscous oil was extracted with two 200-cc. portions of chloroform. The extracts were diluted with 200 cc. of methanol and 5 cc. of concentrated sulfuric acid, then refluxed for about fifteen hours under a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The solution, concentrated to turbidity *in vacuo*, was diluted with 500 cc. of ice-water and the esters extracted with ether. The latter was extracted with two 500-cc. portions of iced 3% sodium hydroxide and the extracts immediately run into iced hydrochloric acid. The mercaptans were extracted with benzene, washed with aqueous sodium bicarbonate and water, then the solvent was evaporated. The residue was fractionated through a Widmer column. The product (XVIII) was obtained as a colorless oil, b.p. 138–142° (1 mm.); yield, 22 g. (14%).

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[8] It is necessary to remove inorganic acids from the crude hydroxy acid, as traces cause acetylation instead of dehydration by acetic anhydride in the next step.

Anal. Calc'd for $C_{12}H_{16}O_3S$: C, 59.9; H, 6.7.
Found: C, 59.7; H, 7.1.

The second fraction, b.p. 155–158° (1 mm.), consisted of 15 g. (8%) of methyl 2-mercapto-5-chlorophenoxyvalerate.

Anal. Calc'd for $C_{12}H_{15}ClO_3S$: C, 52.3; H, 5.5.
Found: C, 52.3; H, 5.6.

A large number of variations of the halogenation were tried without increasing the yield. Bromine gave about the same yields as sulfuryl chloride.

2-(γ-Phenoxypropyl)-3-keto-4-carbomethoxythiophane (XIX). To a mixture of 25.3 g. of methyl 2-mercapto-5-phenoxyvalerate (XVIII) and 0.2 cc. of piperidine was added 13 cc. of methyl acrylate, in portions with ice cooling, so that the temperature was 40–45°. After five hours at room temperature, the mixture was dissolved in 150 cc. of dry ether and added to the dry sodium methoxide obtained by evaporating to dryness *in vacuo* a solution of 2 g. of sodium in methanol. The sodium methoxide rapidly dissolved on swirling. The solution, after sixteen hours at room temperature protected from moisture, was extracted three times with ice-water, the extracts being immediately run into iced hydrochloric acid. The oil was extracted with benzene, washed with aqueous sodium bicarbonate and water. Removal of the solvent *in vacuo* left the keto ester as a yellow-orange oil; yield, 22.7 g. (73%). The keto ester gave a purple color with alcoholic ferric chloride.

Anal. Calc'd for $C_{15}H_{18}O_4S$: C, 61.3; H, 6.2.
Found: C, 61.0; H, 6.5.

The semicarbazone was prepared in dilute methanol and recrystallized from aqueous acetone; white crystals, m.p. 160–161°.

Anal. Calc'd for $C_{16}H_{21}N_3O_4$: C, 54.7; H, 6.0; N, 11.9.
Found: C, 55.0; H, 6 7; N, 11.8.

2-(γ-Chlorophenoxypropyl)-3-keto-4-carbomethoxythiophane. Prepared from methyl 2-mercapto-5-chlorophenoxyvalerate in the same manner as described for XIX, it was an orange oil. The semicarbazone formed white crystals, m.p. 181–182°, when recrystallized from dilute acetone.

Anal. Calc'd for $C_{16}H_{20}ClN_3O_4S$: C, 50.3; H, 5.2; N, 10.9.
Found: C, 50 4; H, 5.6; N, 10.3.

2-(γ-Phenoxypropyl)-3-hydroxythiophane-3,4-dicarboxylic acid (XXI). 2-(γ-Phenoxypropyl)-3-keto-4-carbomethoxythiophane (XIX) was converted to the cyanohydrin and hydrolyzed with 20% sulfuric acid containing no acetic acid in the same manner as for the isomeric hydroxy acid, IXb. The mixture of isomers, obtained in 71% yield, did not crystallize.

Anal. Calc'd for $C_{15}H_{18}O_6S$: C, 55.2; H, 5.5.
Found: C, 55.0; H, 5.6.

The intermediate cyanohydrin, XX, was also analyzed.

Anal. Calc'd for $C_{16}H_{19}NO_4S$: N, 4.4. Found: N, 3.9.

2 (γ-Phenoxypropyl)dihydrothiophene-3,4-dicarboxylic acid. Preparation of Xb. A mixture of 67 g. of 2-(γ-phenoxypropyl)-4-hydroxythiophane-3,4-dicarboxylic acid isomers (IXb) and 330 cc. of acetic anhydride was refluxed for two hours. Most of the acetic anhydride was removed *in vacuo* and the residue heated on the steam-bath with 900 cc. of water for twenty minutes with occasional shaking. The oily acid was extracted with ethyl acetate, washed with dilute hydrochloric acid, and extracted in turn with aqueous sodium bicarbonate. Acidification gave an oil which was extracted with ethyl acetate. The extracts, dried with anhydrous sodium sulfate and clarified with Norit, were evaporated *in vacuo* to give 54 g. (85%) of an amber gum.

One of the isomers was obtained crystalline from benzene and was purified by recrystallization from the same solvent, white crystals, m.p. 133–136°.

Anal. Calc'd for $C_{15}H_{16}O_5S$: C, 58.4; H, 5.2.
Found: C, 58.6; H, 4.7.

Preparation of XXII. From 23.1 g. of 2-(γ-phenoxypropyl)-3-hydroxythiophane-3,4-dicarboxylic acid (XXI) and 120 cc. of acetic anhydride in the same manner as above was obtained 16.8 g. (77%) of an oily, somewhat impure product satisfactory for the next step.

Anal. Calc'd for $C_{15}H_{16}O_5S$: C, 58.4; H, 5.2.
Found: C, 57.8; H, 5.8.

2-Propylthiophane-3,4-trans-dicarboxylic acid (XIa). A mixture of 10 g. of 2-propyldihydrothiophene-3,4-dicarboxylic acid (Xa) and its anhydride was warmed with 42 cc. of 10% sodium hydroxide and 55 cc. of water until solution was complete. The solution was stirred with 150 g. of 2% sodium amalgam at a bath temperature of 70–75° for two hours. The solution, decanted from the mercury, was acidified and the oil extracted with chloroform. The solvent was evaporated and the residue crystallized from benzene-heptane at 0°. The solid was collected on a filter and washed with benzene; yield, 2.9 g. (26%), m.p. 148–153°. For analysis a sample was purified by recrystallization from benzene containing a little acetone, white crystals, m.p. 156–157° which evolve no gas up to 250°.

Anal. Calc'd for $C_9H_{14}O_4S$: C, 49.5; H, 6.4.
Found: C, 49 6, 49.8; H, 5 9, 5.9.

2-(γ-Phenoxypropyl)thiophane-3,4-trans-dicarboxylic acid (XIb). *A.* A solution of 54 g. of 2-(γ-phenoxypropyl)dihydrothiophene-3,4-dicarboxylic acid (Xb) in 350 cc. of water containing 15 g. of sodium hydroxide was stirred with 540 g. of 2% sodium amalgam in the same manner as described for the corresponding propyl compound, XIa, except that ethyl acetate was used for extraction. The crystalline *trans* acid was obtained when the mixture of isomers was triturated with benzene, yield, 16.6 g. (31%), m.p. 169–175°. Recrystallization from acetone-ethylene dichloride gave white crystals, m.p. 182–183°.

Anal. Calc'd for $C_{15}H_{18}O_5S$: C, 58.1; H, 5.8.
Found: C, 58.0; H, 5.5.

B. A solution of 16.8 g. of 2-(γ-phenoxypropyl)dihydrothiophene-3,4-dicarboxylic acid (XXII) in dilute alkali was reduced with sodium amalgam in the same manner as *A*: yield, 4.9 g. (29%), m.p. 175–178°. A mixed m.p. with preparation *A* was 179–181°.

The benzene filtrate (about 100 cc.) was diluted with 50 cc. of absolute ethanol and 1 cc. of concentrated sulfuric acid and refluxed for fifteen hours under a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The solution was washed with water and evaporated *in vacuo.* The residual diester was refluxed with 50 cc. of 1% methanolic sodium methoxide for two hours, then diluted with 10 g. of potassium hydroxide in 100 cc. of water and refluxed three hours more. Most of the methanol was evaporated, the solution diluted with water, acidified, and extracted with ethyl acetate. The ethyl acetate extract was worked up in the same manner as above. An additional 3.4 g. (20%) of *trans* diacid, m.p. 172–178° was obtained. A mixture with preparation *A* melted at 175–180°.

The benzene filtrate was evaporated. The residue consisted of 7 g. of an oil which was probably mainly the second *trans* isomer. It was refluxed with 35 cc. of propionic anhydride for two hours and the excess anhydride removed *in vacuo.* The residue was converted to the dimethyl ester by the previously described continuous drying method. The dimethyl ester was then distilled in a two-bulbed distilling flask at 1 mm., b.p. 180–220°. The dimethyl ester was rearranged and hydrolyzed to the *trans* acids as above. Crystallization from benzene gave 1.2 g. (7%) of *trans* acid, m.p. 175–180°. A mixed m.p. with preparation *A* was 178–181°.

Thus, the total yield of one crystalline *trans* isomer in this reduction was 56%.

2-Propylthiophane-3,4-cis-dicarboxylic acid (XIa). A solution of 1.07 g. of the corresponding crystalline *trans* acid in 5 cc. of propionic anhydride was refluxed for two hours, then the excess anhydride was distilled *in vacuo*. The residue was warmed with 10% aqueous sodium hydroxide until solution was complete. The solution, acidified and saturated with salt, was extracted with ethyl acetate. Removal of the ethyl acetate *in vacuo* left an oil which was crystallized from carbon tetrachloride, yield, 0.61 g. (57%) in two crops, m.p. 127–129° and evolving gas when heated to 150°. Recrystallization from carbon tetrachloride-petroleum ether gave white crystals, m.p. 130–131°.

Anal. Calc'd for $C_9H_{14}O_4S$: C, 49.5; H, 6.4.
Found: C, 49.2; H, 6.6.

2-(γ-Phenoxypropyl)thiophane-3,4-cis-dicarboxylic anhydride. A solution of 500 mg. of 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid (XIb, m.p. 182–183°) in 2.5 cc. of acetic anhydride was refluxed for three hours and the solvent was evaporated *in vacuo*. The residue was distilled in a two-bulbed distilling flask at 1 mm. The distillate partially crystallized. Recrystallization from benzene-petroleum ether gave 240 mg. of white crystals, m.p. 90–98°. Further recrystallization raised the m.p. to 104–105°.

Anal. Calc'd for $C_{15}H_{16}O_4S$: C, 61.7; H, 5.5.
Found: C, 62.4; H, 5.3.

2-(γ-Phenoxypropyl)thiophane-3,4-cis-dicarboxylic acid (XIb). *A.* A warm solution of 50 mg. of pure 2-(γ-phenoxypropyl)thiophane-3,4-*cis*-dicarboxylic anhydride in 10% aqueous sodium hydroxide was acidified. White crystals separated, m.p. 157–158°, and evolved gas at 190°. The m.p. was unchanged on recrystallization from acetone-benzene-petroleum ether.

Anal. Calc'd for $C_{15}H_{18}O_5S$: C, 58.1; H, 5.8.
Found: C, 58.2; H, 5.2.

B. A mixture of 22.8 g. of 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid (XIb, m.p. 169–175°) and 160 cc. of propionic anhydride was refluxed for two hours, then excess anhydride removed *in vacuo*. The residue was warmed with 10% aqueous sodium hydroxide until solution was complete, treated with Norit, and acidified. The oil was extracted with ethyl acetate, the extract washed with dilute hydrochloric acid, and the solvent evaporated *in vacuo*. Trituration of the partially crystalline residue with hot benzene gave 7.7 g. (34%) of white crystals, m.p. 154–156°. The filtrate, on standing overnight, deposited 2.9 g. (13%) of crystals, m.p. 140–143°.

The *cis* diacid, when converted to the methyl ester with diazomethane and boiled with methanolic sodium methoxide, then hydrolyzed with potassium hydroxide, gave the *trans* diacid, m.p. and mixed m p. 183–184°.

2-Propylthiophane-3,4-trans-dicarboxhydrazide (XIIa). *A.* To a suspension of 2 g. of 2-propylthiophane-3,4-*trans*-dicarboxylic acid (XIa) in 20 cc. of ether was added an excess of ethereal diazomethane. The oily ester remaining after evaporation of the ether was refluxed with 15 cc. of methanol and 2 cc. of 85% hydrazine hydrate for one hour. Evaporation *in vacuo* gave 2.1 g. (94%) of product, m.p. 225° dec. Recrystallization from 50% alcohol gave white crystals, m.p. 234° dec.

Anal. Calc'd for $C_9H_{18}N_4O_2S$: C, 43.8; H, 7.4; N, 22.7.
Found: C, 44.1; H, 6.7; N, 22.4.

The configuration of the *trans* dihydrazide was demonstrated by hydrolysis with 6 *N* hydrochloric acid back to 2-propylthiophane-3,4-*trans*-dicarboxylic acid (XIa), m.p. 152–154°. A mixed m.p. was 154–156°.

B. A mixture of 1.05 g. of 2-propyl-3,4-*cis*-dicarbomethoxythiophane and 0.6 cc. of 100% hydrazine hydrate was heated on the steam-bath under reflux for one hour. Trituration with alcohol gave 0.47 g. (45%) of the *trans* dihydrazide, m.p. 203–210° dec.

A large number of experiments were run under various conditions of time, temperature, and solvents, but no *cis* dihydrazide was isolated. The only product which could be obtained was the *trans* dihydrazide in yields varying from 15% to 50% and melting points from

203° to 230° dec. The identity with *trans* dihydrazide was shown by mixed melting points in each case.

2-(γ-Phenoxypropyl)thiophane-3,4-trans-dicarboxhydrazide (*XIIb*). *A*. A suspension of 350 mg. of 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid (XIb) in ether was treated with an excess of ethereal diazomethane. Evaporation left a crystalline methyl ester. It was refluxed for five hours with 10 cc. of Cellosolve and 0.4 cc. of 85% hydrazine hydrate. Removal of the solvent left the crystalline hydrazide which was triturated with benzene; yield, 300 mg. (79%), m.p. 202–204° after recrystallization from aqueous propanol.

Anal. Calc'd for $C_{15}H_{22}N_4O_3S$: N, 16.6. Found: N, 16.5.

When the *trans* dihydrazide was heated at 100° for twenty hours with 10% sulfuric acid, the *trans* diacid (XIb) separated, m.p. and mixed m.p. 181–183°.

B. The dimethyl ester prepared from 0.47 g. of 2-(γ-phenoxypropyl)thiophane-3,4-*cis*-dicarboxylic acid, (XIb) and excess ethereal diazomethane was refluxed with 0.9 cc. of 85% hydrazine hydrate for six hours (bath 130–135°). The cooled mixture was triturated with methanol; yield, 0.17 g. (34%), m.p. 197–204°. A mixed m.p. with preparation *A* showed them to be identical.

No crystalline product other than the *trans* dihydrazide could be isolated by shorter heating periods with or without solvents.

2-Propyl-3,4-trans-dicarbethoxyaminothiophane (*XIIIa*). To a solution of 0.50 g. of 2-propylthiophane-3,4-*trans*-dicarboxhydrazide (XIIa) in 5 cc. of 1 *N* hydrochloric acid and 10 cc. of chloroform was added at 20° dropwise with stirring a solution of 0.30 g. of sodium nitrite in 3 cc. of water over a period of five minutes. After being stirred an additional ten minutes, the chloroform layer was separated and the aqueous layer extracted with chloroform. The combined extracts were dried with calcium chloride at 0°. After dilution with 10 cc. of absolute ethanol, the solution was refluxed one hour, then evaporated to dryness. The residue was triturated with carbon tetrachloride; yield, 0.22 g. (37%) of white crystals, m.p. 170–172°. Recrystallization from ethyl acetate did not change the m.p.

Anal. Calc'd for $C_{13}H_{24}N_2O_4S$: C, 51.3; H, 7.9; N, 9.2.
Found: C, 51.5; H, 7.5; N, 9.3.

When the diazotization was carried out at 0° the yield was 30%.

2-(γ-Phenoxypropyl)thiophane-3,4-trans-dicarbethoxyaminothiophane (*XIIIb*). *A*. From 160 mg. of 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxhydrazide was obtained 70 mg. (37%) of the diurethan, m.p. 172–173° in the same manner as described above for the corresponding 2-propyl compound.

Anal. Calc'd for $C_{19}H_{28}N_2O_5S$: C, 57.7; H, 7.1; N, 7.1.
Found: C, 57 7; H, 6.5; N, 7.2.

B. A mixture of 2.8 g. of 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid (XIb), 10 cc. of benzene, 5 cc. of thionyl chloride, and 1 cc. of a solution of one drop of pyridine in 10 cc. of benzene was refluxed for fifteen minutes, gas evolution being complete in ten minutes. The solution was evaporated *in vacuo*, the residue dissolved in 20 cc. of benzene, and the evaporation repeated. A solution of the residue in 20 cc. of acetone was added dropwise over a period of five minutes to a solution of 2.8 g. of sodium azide in 20 cc. of water at 15–20°. After being stirred one hour the mixture was diluted with 50 cc. of water and the oily azide extracted with chloroform. The extracts, dried with calcium chloride at 0°, were diluted with 25 cc. of absolute ethanol. refluxed thirty minutes, and evaporated. The crystalline residue was heated to boiling with 15 cc. of absolute ethanol, cooled to room temperature and the product collected on a filter; yield, 2.1 g. (58%), m.p. 169–170°. A mixed m.p. with preparation *A* was 170–171°.

trans-4-Methyl-5-(δ-phenoxybutyl)-4,5-dihydro-2-imidazolone. A mixture of 200 mg. of 2-(γ-phenoxypropyl)-3,4-*trans*-dicarbethoxyaminothiophane (XIIb), one-half teaspoon of desulfurizing Raney nickel (18), and 55 cc. of 75% alcohol was refluxed for thirty minutes. The nickel was removed by centrifugation and washed with 20 cc. of acetone. The combined solutions were evaporated to dryness *in vacuo*. The residue was extracted with acetone, separated from a little inorganic material, and evaporated. The residual colorless oil did not crystallize. It was refluxed with 0.5 g. of potassium hydroxide and 2 cc. of methanol for thirty minutes, then diluted with 20 cc. of water. The white crystals had the m.p. 145–147°; yield, 85 mg. (68%). Recrystallization from 50% alcohol raised the m.p. to 148–149°. The ureide is only slightly soluble in hot acetone and contains no sulfur.

Anal. Calc'd for $C_{14}H_{20}N_2O$: C, 67.7; H, 8.1; N, 11.3.

Found: C, 67.6; H, 8.4; N, 11.0.

Recently, Hofmann (19) described the same type of ring closure of a diurethan to an imidazolone by mild hydrolysis.

2-Propylthiophane-3,4-cis-dicarboximide (XXIII). A mixture of 0.50 g. of 2-propylthiophane-3,4-*cis*-dicarboxylic acid (XIa) and 5 cc. of acetyl chloride was refluxed for twenty minutes. Evaporation *in vacuo* gave an oily anhydride. After the addition of 1 cc. of 28% ammonia water the solution was heated on the steam-bath for thirty minutes, then at 160° for one hour. The mixture was cooled and diluted with water; yield 0.35 g. (77%), m.p. 86–90°. Recrystallization from benzene-petroleum ether with the aid of Norit gave white crystals, m.p. 94–96°.

Anal. Calc'd for $C_9H_{13}NO_2S$: N, 7.0. Found: N, 6.9.

A solution of 170 mg. of the *cis* imide (XXIII) in 0.4 cc. of 85% hydrazine hydrate was heated on the steam-bath under reflux for fifteen hours. The solid was triturated with methanol; yield, 110 mg., of 2-propylthiophane-3,4-*trans*-dicarboxhydrazide, m p. 240° dec. which was identified by a mixed m.p.

Several attempted Hofmann degradations with aqueous or methanolic sodium hypobromite gave no crystalline products.

2-Propylthiophane-3,4-cis-dicarboxy-N,N'-monohydrazide (XXIV). To the anhydride from 0.50 g. of 2-propylthiophane-3,4-*cis*-dicarboxylic acid (XIa) prepared as above with acetyl chloride was added 0.5 cc. of 85% hydrazine hydrate. The solution was dissolved in 20 cc. of water, acidified with 2 cc. of acetic acid, and heated on the steam-bath for fifteen minutes. The cooled solution was extracted twice with benzene, the extracts washed with aqueous sodium bicarbonate, and concentrated to 5 cc. Dilution with petroleum ether gave 0.25 g. (50%) of product, m.p. 76–79°. Recrystallization from benzene-petroleum ether gave white crystals, m.p 81–82°.

Anal. Calc'd for $C_9H_{14}O_2N_2S$: N, 13.1. Found: N, 13.2.

The cyclic hydrazide structure (XXIV) was assigned on the basis of solubility in aqueous alkali and insolubility in 1 *N* hydrochloric acid or dilute sodium bicarbonate solution.

A mixture of 120 mg. of the cyclic hydrazide (XXIV) and 0.4 cc. of 85% hydrazine hydrate was heated on the steam-bath for two hours Trituration with methanol gave white crystals, m.p. 232° dec., identical with 2-propylthiophane-3,4-*trans*-dicarboxhydrazide (XIIa). When the same reaction was carried out in 5 cc. of butanol at the b.p. as a solvent, starting material was the only compound which could be isolated.

2-Propyl-3,4-trans-diaminothiophane sulfate. To a filtered solution of 3 g. of barium hydroxide in 15 cc. of water was added 0.52 g. of 2-propyl-3,4-*trans*-dicarbethoxyaminothiophane (XIIIa) in 10 cc. of methanol. After being refluxed for twenty-four hours, the mixture was just acidified with dilute sulfuric acid, and the filtered solution evaporated to dryness *in vacuo*. Trituration with acetone gave 0.28 g. (64%) of white crystals which were recrystallized from water. The sulfate gradually decomposes above 300° without melting.

Anal. Calc'd for $C_7H_{18}N_2O_4S_2$: C, 32 6; H, 7.0; N, 10.8; $SO_4^=$, 37.2.

Found: C, 32.9; H, 6.6; N, 10.8; $SO_4^=$, 36.8.

Action of 48% hydrobromic acid on 2-(γ-phenoxypropyl)-3,4-trans-dicarbethoxyaminothiophane (XIIIb). A mixture of 1.7 g. of the urethan and 25 cc. of 48% hydrobromic acid was refluxed under an air condenser for two hours, then evaporated to dryness *in vacuo*. The residue solidified on trituration with absolute alcohol; yield, 1.4 g. For analysis a sample of the bromide was dissolved in water and precipitated by the addition of absolute alcohol, m.p., gradually decomposes over 200°.

Anal. Calc'd for $C_7H_{16}Br_2N_2S$ (XXVI): C, 26.3; H, 5.0; N, 8.8; Br^-, 50.0.
Calc'd for $C_7H_{17}Br_3N_2S$ (XXVII): C, 21.0; H, 4.3; N, 7.0; Br^-, 59.8.
Found: C, 22.9; H, 4.9; N, 7.4; Br^-, 54.1, 54.7.

This material gave no water-insoluble derivatives when treated with (a) phosgene in aqueous sodium carbonate at 0°; (b) sodium acetate in acetic anhydride; (c) sodium acetate, acetic anhydride, and water; (d) aqueous sodium hydroxide and phenyl isothiocyanate; (e) aqueous picric acid; (f) formamide by fusion; or (g) benzoyl chloride in triethylamine.

Dibenzoyl derivative of 3-aminopiperidino[3,2,b]thiophane (XXVI). To a solution of 410 mg. of the above mixture in 3 cc. of 10% sodium hydroxide was added 0.3 cc. of benzoyl chloride. The mixture was shaken at about 35° until the benzoyl chloride had reacted, then treated again with 3 cc. of 10% sodium hydroxide and 0.3 cc. of benzoyl chloride. The dibenzoyl derivative was removed by filtration and the filtrate treated twice more with alkali and benzoyl chloride. In this way a total of 240 mg. of product, m.p. 147–151° was obtained. It was purified by recrystallizations from dilute alcohol, m.p. 165–166°. This compound contained no bromine.

Anal. Calc'd for $C_{21}H_{22}N_2O_2S$: C, 68.8; H, 6.0; N, 7.7; M.W., 366.
Found: C, 68.4; H, 5.5; N, 7.8; M.W. (Rast), 357.

1,2-Trimethylene-3,4-trans-dicarboxythiophanium bromide (XXVIII). A solution of 0.20 g. of 2-(γ-phenoxypropyl)thiophane-3,4-*trans*-dicarboxylic acid (XIb) in 2 cc. of 48% hydrobromic acid was refluxed for twenty minutes, then evaporated to dryness *in vacuo*. The evaporation was repeated with 5 cc. of water and then with 5 cc. of absolute ethanol. The residue, on trituration with acetone, crystallized to a white solid, m.p. about 170° with decomposition; yield, 0.11 g. (59%). This compound is extremely soluble in water. No suitable solvent could be found for recrystallization.

Anal. Calc'd for $C_9H_{13}BrO_4S$: Br^-, 26.9. Found: Br^-, 28.0.

SUMMARY

Two isomeric methods of synthesizing 2-alkylthiophane-3,4-dicarboxylic acids have been described.

Curtius degradations of the 2-alkylthiophane-3,4-*trans*-dicarboxylic acids have led to derivatives of the corresponding 3,4-*trans*-diamines, but *cis* diamines could not be obtained from the *cis* diacids.

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[Contribution from the Department of Biochemistry, Cornell University Medical College, and from The Lederle Laboratories]

BIOTIN. II. 3,4-*trans*-DIAMINOTHIOPHANE

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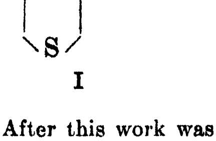
The syntheses of two isomeric 3,4-diaminothiophanes have been previously reported by one of these laboratories. Curtius degradation (1) of a thiophane-3,4-dicarboxhydrazide (II) yielded the diurethan (III) of a 3,4-diaminothiophane, both of unknown configuration. A second isomer of 3,4-diaminothiophane was synthesized (2) by the treatment of a 2,3-diaminobutane-1,4-disulfuric acid with sodium sulfide.

Through the characterization of the *cis*- and *trans*- forms of thiophane-3,4-dicarboxylic acid (I), it has now been demonstrated that the dihydrazide, II, and diurethan, III, have a *trans* relationship of the 3,4-substituents. The isomer of 3,4-diaminothiophane obtained in the second synthesis (2) must therefore have the *cis* configuration.

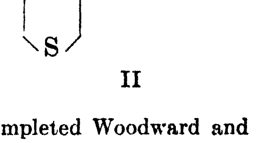
The thiophane-3,4-dicarboxylic acids (I) were prepared by extension of the earlier method from 3,3,4,4-tetracarbethoxythiophane (1) and by the recently described general method from 3-keto-4-carbethoxythiophanes (3). The identity of the dicarboxylic acids, I, synthesized by each method proves that under the conditions employed, the Dieckmann cyclization[1] of ethyl β-(carbethoxymethylthio)propionate takes place predominately in the desired direction.

3-Carbethoxy-4-ketothiophane was converted to the cyanohydrin and dehydrated with phosphorus oxychloride in pyridine to 3-carbethoxy-4-cyanodihydrothiophene. Acid hydrolysis resulted in a dihydrothiophene-3,4-dicarboxylic acid which was smoothly reduced with sodium amalgam in dilute aqueous alkali to a mixture of the *cis* and *trans* isomers of thiophane-3,4-dicarboxylic acid (I).

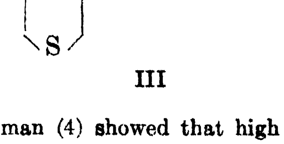
Esterification of the *cis-trans* diacid mixture and inversion by sodium methoxide followed by hydrolysis resulted in the formation of the pure *trans* diacid, m.p. 140–141°. The identical *trans* diacid was also obtained by cold alkaline hydrolysis of 3,4-dicarbethoxythiophane prepared by the earlier method (1). Acid hydrolysis of this diester gave a mixture of *cis* and *trans* isomers.



I



II



III

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[1] After this work was completed Woodward and Eastman (4) showed that high temperature Dieckmann cyclization of methyl β-(carbomethoxymethylthio)propionate yielded 3-carbomethoxy-4-ketothiophane whereas low temperatures favored the formation of 2-carbomethoxy-3-ketothiophane.

The mixture of *cis* and *trans* diacids from either source, when treated with acetyl chloride and then evaporatively distilled at 150° *in vacuo* gave the same thiophane-3,4-*cis*-dicarboxylic anhydride, m.p. 84–85°, which was easily hydrolyzed to the *cis* diacid, I, m.p. 134–135°. The latter, with acetyl chloride, readily reformed the *cis* anhydride in contrast to the *trans* diacid which gave a polymeric or mixed anhydride.

Esterified and treated with hydrazine, thiophane-3,4-*trans*-dicarboxylic acid (I) gave the corresponding *trans*-dihydrazide (II). That no inversion of configuration took place was demonstrated by acid hydrolysis back to the original *trans* diacid. However, when the *cis*-diacid was treated under the same conditions, the *trans*-dihydrazide was again formed, inversion of configuration having taken place.

Therefore, the 3,4-diaminothiophane synthesized from the *trans*-dihydrazide (II) must also have the *trans* configuration, as Curtius degradation has been reported to proceed without inversion (5). These results are similar to those obtained from the 2-alkylthiophane-3,4-dicarboxylic acids (3).

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EXPERIMENTAL

Ethyl β-(carbethoxymethylthio)propionate. To a mixture of 228 g. of ethyl thioglycolate (3) and 2 cc. of piperidine was added 350 cc. of ethyl acrylate in portions with ice cooling so that the temperature was 30–40°. An additional 2 cc. of piperidine was added in two portions after ten and twenty minutes. At the end of fifteen hours the mixture was distilled: colorless oil, b.p. 154–155° (12 mm.); yield 407 g. (97%).

The ethyl acrylate may be reduced to a 5% excess without appreciable lowering of the yield, but a 1:1 ratio gives only 90%.

After this work was completed, Buchman and Cohen (7) as well as Woodward and Eastman (4) mentioned this method but gave no experimental details. The b.p. of this compound has been recorded as 148–150° (10 mm.) by Karrer and Schmidt (6).

3-Carbethoxy-4-ketothiophane. *A.* To the dry sodium ethoxide from 2 7 g. of sodium, obtained by evaporating an ethanolic solution to dryness *in vacuo*, was added 20.4 g. of ethyl β-(carbethoxymethylthio)propionate in 100 cc. of dry benzene. The mixture was distilled from a bath at 125° through a Vigreux column. In thirty minutes 70 cc. of distillate, b.p. 68–78°, was obtained, distillation stopped, and the solid sodium enolate began to separate. After thirty minutes more at 125°, the mixture was cooled in an ice-bath and diluted with ice-water and ether. The aqueous layer was acidified with acetic acid and the ether layer extracted once more with water. The combined acidified extracts were in turn extracted with benzene, washed successively with water, dilute sodium bicarbonate and water. Distillation gave 7.7 g. (48%) of a colorless liquid, b.p. 90–93° (1 mm.).

Anal Calc'd for $C_7H_{10}O_3S$: C, 48.2; H, 5.8; S, 18.4.
Found: C, 48.2; H, 5.7; S, 18.3.

The semicarbazone formed white needles from dilute ethanol, m p. 171–173°.

Anal. Calc'd for $C_8H_{13}N_3O_3S$: C, 41.5; H, 5.7; N, 18.2.
Found: C, 41 6; H, 6.1; N, 17.6.

After this work was completed Buchman and Cohen (7) reported the b.p. of the keto ester as 96° (4 mm.) and the m.p. of the semicarbazone as 176°, but gave no experimental details.

B. To the dry sodium ethoxide from 17 5 g. of sodium was added 82.5 g. of ethyl thioglycolate in 200 cc. of benzene. Most of the sodium ethoxide dissolved on shaking. To the mixture was added dropwise with shaking, 77 cc. of ethyl acrylate over a period of ten minutes. After being refluxed for two and one-half hours, the benzene solution was extracted with ice-water and worked up as in part *A*; yield, 68 g. (48%), b.p. 105–122° (5 mm.), but mainly at 110–115°.

The cyclization can also be carried out on ethyl β-(carbethoxymethylthio)propionate with sodium ethoxide in boiling benzene for two hours; yield, 55% of a product boiling at 107–111° (6 mm.).

3-Carbethoxy-4-cyanodihydrothiophene. To 40 cc. of liquid hydrogen cyanide (3) and 0.5 cc. of 50% potassium hydroxide solution cooled in an ice-bath was added 130 g. of 3-carbethoxy-4-ketothiophane in portions so that the temperature was maintained at 5–15°. After twenty hours at 0–5° the mixture was acidified with 1.5 cc. of 85% phosphoric acid and the excess hydrogen cyanide was removed *in vacuo*. The residue, dissolved in 200 cc. of benzene, was dried with sodium sulfate and the drying agent rinsed with 170 cc. of benzene. The solution was diluted with 370 cc. of dry pyridine and 160 cc. of phosphorus oxychloride was added. The temperature was maintained at 40–45° with occasional cooling until the reaction was no longer exothermic. After a total of six hours the mixture was poured into iced hydrochloric acid, the organic layer was washed with dilute hydrochloric acid, iced 3% sodium hydroxide, dilute acetic acid, and then distilled. The product, b.p. 122–125° (1 mm.), partially solidified in the receiver; yield, 114 g. (84%).

Anal. Calc'd for $C_8H_9NO_2S$: C, 52.5; H, 5.0; N, 7.6.
Found: C, 52.7; H, 4.8; N, 7.1.

Dihydrothiophene-3,4-dicarboxylic acid. A mixture of 113 g. of 3-carbethoxy-4-cyanodihydrothiophene, 230 cc. of acetic acid, and 560 cc. of concentrated hydrochloric acid was refluxed for thirteen hours, diluted to 2 l. with water and clarified with Norit. Saturated with salt, the solution was extracted with three 500-cc. portions of ethyl acetate. The extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo* and the residue was crystallized from benzene; yield 79 g. (71%), m.p. 165–180°. Recrystallization from acetone-benzene gave white crystals which melted at 169–185°. This may be a mixture of isomers.

Anal. Calc'd for $C_6H_6O_4S$. C, 41.3; H, 3.4; S, 18.4.
Found: C, 41.6; H, 2.7; S, 18.4.

cis and trans-Thiophane-3,4-dicarboxylic acids (*I*). A solution of 300 g. of dihydrothiophene-3,4-dicarboxylic acid in 2600 cc. of 5% sodium hydroxide was stirred with 4.6 kg. of 2% sodium amalgam. The heat of reaction raised the temperature to 75° for about thirty minutes. The mixture was stirred ninety minutes more at 70–80°. The decanted solution was acidified, saturated with salt and extracted three times with ethyl acetate. The solvent was removed *in vacuo* and the residue was crystallized from benzene, white crystals, m.p. 102–120°; yield, 260 g. (87%) of a mixture of *cis* and *trans* isomers.

Thiophane-3,4-trans-dicarboxylic acid (*I*). *A*. A mixture of 5.5 g. of 3,4-dicarbethoxythiophane, obtained by the bis-malonic ester method (1), 1.9 g. of sodium hydroxide, 35 cc. of water, and 5 cc. of alcohol was allowed to stand at room temperature for three hours, then acidified and continuously extracted with benzene. Concentration gave 3.7 g. (82%) of the *trans* acid in the form of white leaflets, m.p. 131–134°, resolidifies and remelts at 140–141° (cor.). Recrystallization from acetone-benzene did not change the m.p. After standing for eighteen months the acid had changed over completely to the high-melting form, m.p. 140–141°.

Anal. Calc'd for $C_6H_8O_4S$: C, 40.8; H, 4.6.
Found: C, 40.9; H, 4.7.

When this same diester was hydrolyzed by boiling with dilute ethanolic hydrochloric acid, a mixture of *cis* and *trans* isomers, m.p. 110–124°, was obtained.

B. A solution of 25 g. of thiophane-3,4-dicarboxylic acid (m.p. 102–120°, obtained by reduction of dihydrothiophene-3,4-dicarboxylic acid) and 2.5 cc. of concentrated sulfuric acid in 100 cc. of absolute ethanol and 100 cc. of benzene was refluxed twenty-four hours under a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. After being washed with water, the solution was evaporated *in vacuo*. The residue was refluxed for one hour with 60 cc. of absolute ethanol containing 1.5 g. of sodium, then diluted with 25 g. of potassium hydroxide in 75 cc. of water and refluxed an additional hour. Acidified with 60 cc. of concentrated hydrochloric acid, the solution was extracted with 300 cc. of ethyl acetate in three portions and the extracts dried with magnesium sulfate. Evaporation *in vacuo* and trituration with benzene gave 21.5 g. (85%) of *trans* acid, m.p. 133–136°.

A similar preparation was recrystallized from acetone-benzene, white leaflets, m.p. 132–134°, resolidifies and remelts at 139–141° (uncor.). A mixture of the latter with preparation *A* gave no depression in m.p.

Thiophane-3,4-cis-dicarboxylic anhydride. A mixture of 1.5 g. of thiophane-3,4-dicarboxylic acid (m.p. 105–116°, obtained above by acid hydrolysis method *A*) and 15 cc. of acetyl chloride was refluxed for five hours, solution being complete in fifteen minutes. After removal of the volatile material *in vacuo*, the residue was evaporatively distilled for ten hours at 150° and 20 mm. onto a cold finger; white crystals, m.p. 84–85° (cor.); yield, 0.70 g. (50%).

Anal. Calc'd for $C_6H_6O_3S$: C, 45.6; H, 3.8.
Found: C, 45.5; H, 3.7.

Similarly, the mixed isomeric thiophane-3,4-dicarboxylic acids obtained by reduction of dihydrothiophene-3,4-dicarboxylic acid gave the same anhydride, m.p. and mixed m.p. 83–84°.

Thiophane-3,4-cis-dicarboxylic acid (I). A sample of the corresponding *cis*-anhydride was heated with a little water until solution was complete, then evaporated to dryness *in vacuo*. The residue was recrystallized from acetone-benzene, white blades, m.p. 134–135° (cor.). A mixed m.p. with thiophane-3,4-*trans*-dicarboxylic acid was 105–109°.

Anal. Calc'd for $C_6H_8O_4$: C, 40.8; H, 4.6.
Found: C, 40.8; H, 4.3.

A few mg. of the *cis*-acid was refluxed for one hour with 1 cc. of acetyl chloride. Evaporation and trituration with benzene gave the *cis*-anhydride, m.p. 82–85°. The *cis*-diacid was again regenerated by water treatment. On the other hand the pure *trans*-acid gives a polymeric or mixed anhydride with acetyl chloride which gives the *trans* acid on hydrolysis. The mixed anhydride when heated to 150° is rearranged to the *cis*-anhydride.

Thiophane-3,4-trans-dicarboxhydrazide (II). A. A solution of 500 mg. of thiophane-3,4-*trans*-dicarboxylic acid in 2 cc. methanol was treated with an excess of ethereal diazomethane. The solution was evaporated and the residue refluxed for thirty minutes with 1 cc. of 100% hydrazine hydrate in 5 cc. of absolute ethanol. During this time the product separated from solution. The mixture was diluted with 5 cc. of absolute ethanol, cooled in an ice-bath and the dihydrazide collected on a filter; yield, 450 mg. (80%) of white needles, m.p. 223–224°. Admixture with the thiophane-3,4-dicarboxhydrazide previously described (1) gave no depression in the m.p.

A solution of 230 mg. of the above hydrazide in 4 cc. of 6 *N* hydrochloric acid was heated on the steam-bath under reflux for twenty-four hours. After dilution with 10 cc. of water and saturation with salt, the solution was extracted twice with ethyl acetate. The dried extracts were evaporated *in vacuo* and the residue crystallized from benzene, white leaflets, m.p. 131–134°, resolidifies and remelts at 138–139°; yield, 165 mg. (83%). A mixed m.p. with thiophane-3,4-*trans*-dicarboxylic acid was the same, while a mixed m.p. with the *cis*-diacid was 87–96°, thus indicating the *trans* configuration of the hydrazide.

B. When 20 mg. of thiophane-3,4-*cis*-dicarboxylic acid was esterified with diazomethane and treated with hydrazine under the same conditions used for *trans* ester, the *trans*-hydrazide, m p. 218–220°, was obtained. It gave no depression in m.p. when mixed with preparation *A*.

3,4-trans-Diaminothiophane dihydrobromide. A mixture of 1.0 g. of 3,4-*trans*-dicarbethoxyaminothiophane (1) and 10 cc. of 48% hydrobromic acid was refluxed for forty minutes. In five minutes solution was complete and in ten minutes the product began to crystallize out. The mixture was cooled to 5°, the product collected on a glass filter and washed with alcohol and ether, white crystals, m.p. > 350°; yield, 1.05 g. (95%).

Anal. Calc'd for $C_4H_{12}Br_2N_2S$: N, 10.0. Found: N, 9.8.

The dihydrobromide is readily soluble in cold water, insoluble in cold 48% hydrobromic acid, hot alcohol, or hot acetic acid. It is somewhat soluble in hot 48% hydrobromic acid.

3,4-trans-Diuramidothiophane. A solution of 100 mg. of 3,4-*trans*-diaminothiophane dihydrobromide and 90 mg. of potassium cyanate in 2 cc. of water was allowed to stand at room temperature for eight hours. The white leaflets were removed by filtration and recrystallized from 50% alcohol, m.p. 249–250° dec.; yield, 70 mg. (83%).

Anal. Calc'd for $C_6H_{12}N_4O_2S$: N, 27.4. Found: N, 27.6.

SUMMARY

The *cis* and *trans* forms of thiophane-3,4-dicarboxylic acids have been characterized.

The configuration of one of the previously known 3,4-diaminothiophanes has been established as *trans*.

NEW YORK, N. Y.
PEARL RIVER, N. Y.

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[Contribution from the Department of Biochemistry, Cornell University Medical College, and the Lederle Laboratories]

BIOTIN. III. 2-(δ-CARBOXYBUTYL)THIOPHANE-3,4-DICARBOXYLIC ACID[1]

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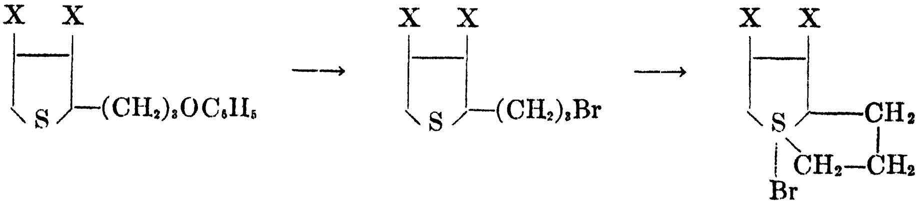
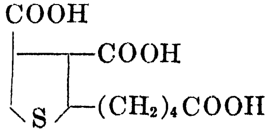
It was recently demonstrated (1) that hydrobromic acid hydrolysis of a 2-(γ-phenoxypropyl)thiophane substituted by amine or carboxyl groups in the 3 and 4 positions (I) failed to give the expected 2-(γ-bromopropyl)thiophane derivatives (II) because the latter apparently suffered ring closure to sulfonium bromides (III).



I II III

Since the valeric acid side chain of biotin could not be completed by a method involving the halogenated thiophane, II, it became apparent that the proper side chain should be present in the molecule before introducing the sulfur atom.[2] The synthesis of 2-(δ-carboxybutyl)thiophane-3,4-dicarboxylic acid (IV) was accomplished by one of the general methods recently described (1).



IV

Rosenmund reduction of ethyl adipyl chloride (V) took place readily to ethyl 5-formylvalerate (VI). By condensation of the aldehyde with malonic acid, 7-carbethoxy-2-heptenoic acid (VII) was obtained as an oil. It was best purified by saponification to the corresponding diacid, VIII. Esterification gave pure methyl 7-carbomethoxy-2-heptenoate (IX), which added methyl thioglycolate smoothly in the presence of piperidine to give a good yield of methyl 3-(carbomethoxymethylthio)suberate (X).

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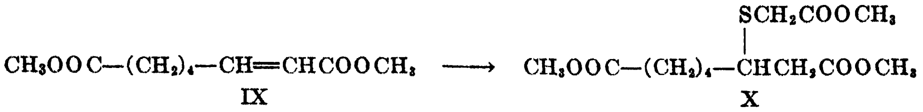
[1] Because of the pressure of certain researches necessitated by the war effort the Cornell group suspended work on the problem at this point.

[2] After completion of this work, Grüssner, Bourguin, and Schnider (9a) published a synthesis of two empirical isomers of *dl*-biotin as well as *dl*-biotin in minute yield by the use of a methoxybutyl side chain. These isomers were not structural isomers of biotin (9b). This may possibly be explained by formation of a thiophanium bromide (1) and subsequent ring opening to an isomeric structure. *cf.* Bennet and Hock (10).

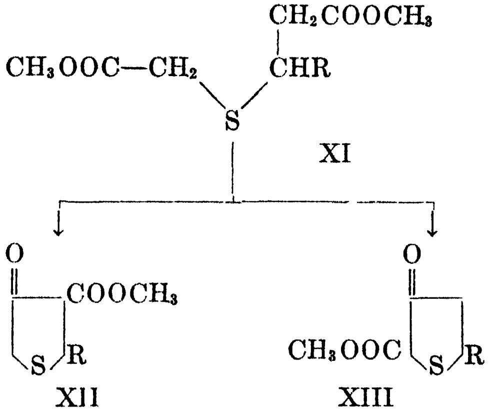
$$\underset{\text{V}}{C_2H_5OOC\text{—}(CH_2)_4\text{—}COCl} \longrightarrow \underset{\text{VI}}{C_2H_5OOC\text{—}(CH_2)_4\text{—}CHO} \longrightarrow$$

$$\underset{\text{VII}}{C_2H_5OOC\text{—}(CH_2)_4\text{—}CH{=}CHCOOH} \rightarrow \underset{\text{VIII}}{HOOC\text{—}(CH_2)_4\text{—}CH{=}CHCOOH} \rightarrow$$



$$\underset{\text{IX}}{CH_3OOC\text{—}(CH_2)_4\text{—}CH{=}CHCOOCH_3} \longrightarrow \underset{\text{X}}{CH_3OOC\text{—}(CH_2)_4\text{—}\overset{\displaystyle SCH_2COOCH_3}{\overset{|}{C}}HCH_2COOCH_3}$$

It was previously shown (1, 2) that Dieckmann cyclization of an ester of type XI, which can form either XII or XIII, gave predominately XII when R was $-C_3H_7(n)$, $-(CH_2)_3OC_6H_5$ or H provided the reaction was carried out in boiling benzene.



However, when R was $-(CH_2)_4COOCH_3$ the cyclization with sodium methoxide in hot toluene gave two fractions, one an insoluble crystalline sodium enolate and the other a soluble sodium enolate in yields of 61% and 13% respectively. The soluble fraction gave a keto ester which was mainly XII, while the crystalline insoluble fraction appeared to be XIII. These conclusions were supported by the following evidence:

The keto ester from the soluble sodium enolate fraction was converted to the cyanohydrin with liquid hydrogen cyanide and dehydrated with phosphorus oxychloride and pyridine in benzene to 2-(δ-carbomethoxybutyl)-3-carbomethoxy-4-cyanodihydrothiophene. Acid hydrolysis followed by sodium amalgam reduction gave crystalline 2-(δ-carboxybutyl)thiophane-3,4-*trans*-dicarboxylic acid (IV). The choice between IV and 2-(δ-carboxybutyl)thiophane-4,5-dicarboxylic acid (derived from XIII) was established by the identity of the product with a sample of the triacid (IV) synthesized by an unequivocal method (3). When the keto ester from the insoluble crystalline sodium enolate fraction was carried through the same sequence of reactions, no crystalline triacid could be isolated.

Subsequently, Woodward and Eastman (4) observed that 3-keto-4-carbomethoxythiophane (XII, R = H) gave a permanent red-violet color with ferric chloride, whereas 2-carbomethoxy-3-ketothiophane (XIII, R = H) gave a transitory color with ferric chloride. They showed that the latter was quantitatively oxidized by ferric chloride to a double compound, $C_{12}H_{14}O_6S_2$.

When these observations were applied to the keto ester fractions obtained by cyclization of methyl β-(carbomethoxymethylthio)suberate (X), it was found that the keto ester obtained from the insoluble sodium enolate fraction gave a transitory green color with ferric chloride and 97% of the theoretical amount necessary to cause oxidation to a double compound was consumed before a permanent color was obtained (using acetoacetic ester as an indicator), indicating that this keto ester fraction was pure XIII.

The keto ester from the soluble sodium enolate fraction, which gave a transitory purple color with ferric chloride, was titrated in the same manner. Only 45% of the theoretical amount of ferric chloride was consumed, thus indicating that this fraction was a mixture of XII and XIII in a ratio of about 1:1. The keto ester, XII, remaining after the oxidation was isolated by means of its solubility in alkali. It gave a permanent purple color with ferric chloride[3] and formed a semicarbazone, m.p. 127–129°. This was isomeric with the semicarbazone, m.p. 128–129°, of the keto ester, XIII, obtained from the insoluble sodium enolate fraction. A mixture of the two gave a depression in the melting point.

The crystalline triacid, IV, was shown to have a *trans* configuration of the carboxyl groups by treatment successively with thionyl chloride and aniline. A trianilide was obtained. If the configuration were *cis*, a mono acid chloride anhydride would have been formed (1) which would result in an alkali-soluble monoanilide anilic acid derivative on subsequent treatment with aniline.

The crystalline triacid, IV, was also obtained *via* conversion of 7-carbethoxy-2-heptenoic acid (VII) to the diethyl ester. However, no insoluble sodium enolate fraction was obtained in the Dieckmann cyclization. The crystalline triacid, IV, was difficult to isolate and in some runs none could be crystallized.

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EXPERIMENTAL

Ethyl hydrogen adipate. The method of Swann, Oehler, and Buswell (5) was modified for large runs in order to avoid the fractional distillation. A much purer product, m.p. 28–29°, was obtained.

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[3] Of the nine derivatives of 3-carboxalkyl-4-ketothiophane of known structure described in the literature or prepared in this laboratory, all give red-brown, red-violet, or purple colors with ferric chloride. On the other hand, eight derivatives of 2-carboxalkyl-3-ketothiophane all give green or blue ferric chloride tests. No exceptions have yet been observed. This color test may possibly be used to distinguish between structurally isomeric keto esters. Application to the keto esters under consideration gave results which are in agreement with the other lines of evidence for their structures.

A mixture of 1160 g. of adipic acid, 940 g. of ethyl adipate, 620 cc. of commercial absolute ethanol, 400 cc. of dibutyl ether, and 200 cc. of concentrated hydrochloric acid was refluxed for four and one-half hours. Volatile material was removed on the steam-bath *in vacuo*, the hot residue was diluted with 1 liter of benzene, then cooled overnight at 5°. The white crystals of adipic acid were washed with 500 cc. of benzene in portions; weight, 310 g.

The filtrate was added in a thin stream to a stirred mixture of 850 g. of sodium bicarbonate and 6 l. of water. After being stirred an additional ten minutes, the layers were separated. Distillation of the benzene layer gave 850 g. of unchanged ethyl adipate.

The aqueous bicarbonate solution was covered with 500 cc. of benzene and acidified with 900 cc. of concentrated hydrochloric acid with stirring. Distillation of the benzene extract gave 920 g. (66% or 84% based on the adipic acid and ethyl adipate not recovered) of white crystals, m.p. 28–29°, b.p. 140–145° (2 mm.).

Blaise and Koehler (6) give the m.p. 29° and b.p. 160° (7 mm.).

Ethyl adipyl chloride (*V*). This was prepared in the usual manner with thionyl chloride in 99% yield, b.p. 120° (15 mm.). Blaise and Koehler (6) record b.p. 128° (17 mm.).

Ethyl 5-formylvalerate (*VI*). A mixture of 300 g. of ethyl adipyl chloride, 28 g. of 5% palladium-barium sulfate catalyst, 1 cc. of quinoline-sulfur poison (7) and 1 liter of xylene was stirred under reflux at a bath temperature of 130–140° while a stream of hydrogen was bubbled through the solution. At the end of four hours 85% of the theoretical amount of hydrogen chloride had been evolved and reduction was slow. After removal of the catalyst, the xylene was removed *in vacuo* and the residue distilled until the distillation became slow, b.p. 90–93° (2 mm.); yield, 147 g. (58%) of a colorless liquid.

A similar preparation had the following physical constants: b.p. 111–116° (14 mm.); n_D^{24} 1.4300; d_{23}^{23} 1.000; M_D (Calc'd) 40.8; M_D (found), 40.8.

By continued distillation impure aldehyde was slowly obtained which was dissolved in ether, washed with aqueous sodium bicarbonate, dried, and redistilled. In this way another 10–15% of aldehyde was obtained. The aldehyde is 60% polymerized after one week at 5° and should be used as soon as possible.

The 2,4-dinitrophenylhydrazone was obtained as either one of two modifications from ethanol, m.p. 59–60° or 74–75°. The lower-melting form after melting is converted to the higher-melting form. A mixture of the two melts at 74–75°.

Anal. Calc'd for $C_{14}H_{18}N_4O_6$: N, 16 6.
Found (m.p. 59–60°): N, 16.7.
Found (m.p. 74–75°): N, 16.7.

After this compound was prepared Baer (8) synthesized it by another method. He gives the physical constants of the aldehyde, b.p. 97–98° (10 mm.), n_D^{24} 1.4280, and m.p. 74–75° for its 2,4-dinitrophenylhydrazone.

7-Carboxy-2-heptenoic acid (*VIII*). To a mixture of 124 g. of ethyl 5-formylvalerate (VI), 160 g. of malonic acid, and 180 cc. of pyridine was added 4 cc. of piperidine. After standing overnight the solution was poured into dilute hydrochloric acid and extracted with benzene. The benzene extract was extracted in turn with aqueous sodium bicarbonate. Acidification gave an oil which was taken up in benzene and washed with water. Evaporation gave 90 g. (57%) of 7-carbethoxy-2-heptenoic acid (VII) as an oil.

A solution of 86 g. of the monoester in 500 cc. of water containing 90 g. of sodium hydroxide was heated on the steam-bath for two hours, then poured into ice and 200 cc. of concentrated hydrochloric acid. The white solid was washed with water; yield, 48.7 g. (66%), m.p. 186–189° (uncor.). Recrystallization from water raised the m.p. to 196–198° (cor.)

Anal. Calc'd for $C_8H_{12}O_4$: C, 55.8; H, 7.0.
Found: C, 55.2; H, 6.9.

This acid was characterized by catalytic reduction in ethanol with Adams catalyst to suberic acid, m.p. and mixed m.p. 141.5–143° (cor.).

Methyl 7-carbomethoxy-2-heptenoate (*IX*). A solution of 48.7 g. of 7-carboxy-2-heptenoic acid (VIII) in 200 cc. of chloroform and 150 cc. of methanol containing 2 cc. of concentrated sulfuric acid was refluxed for sixteen hours under a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The solution, washed with water, was distilled. The product was a water-white liquid, b.p. 148° (11 mm.); yield, 52.5 g. (93%).

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1.
Found: C, 60.4; H, 8.4.

Methyl β-(carbomethoxymethylthio)suberate (*X*). To a mixture of 52 g. of methyl 7-carbomethoxy-2-heptenoate (IX) and 28 cc. of methyl thioglycolate was added 0.5 cc. of piperidine. The temperature was maintained at 43–48° by adequate cooling. After standing for fifteen hours, the mixture was distilled; colorless oil, b.p. 198° (1 mm.) (bath 230°); yield, 74.1 g. (93%). The b.p. varied considerably with the bath temperature.

Anal. Calc'd for $C_{13}H_{22}O_6S$: C, 50.9; H, 7.3.
Found: C, 50 2; H, 6.9.

2-(δ-Carbomethoxybutyl)-4-keto-3 and 5-carbomethoxythiophane [*XII and XIII, R* = $-(CH_2)_4COOCH_3$]. To a suspension of 5.4 g. of sodium methoxide (Mathieson) in 50 cc. of toluene was added 25 g. of methyl β-(carbomethoxymethylthio)suberate (X) in 25 cc. of toluene. The solution was refluxed on the steam-bath for one hour. In a few minutes a crystalline sodium enolate had separated from solution. The mixture was cooled, the solid removed and washed with toluene. The solid was shaken with iced hydrochloric acid and benzene containing a little toluene until solution was complete. The organic layer was separated, washed with aqueous sodium bicarbonate and water. Removal of the solvent *in vacuo* left 13.7 g. (61%) of XIII as a colorless oil, which gave a transitory green color with alcoholic ferric chloride.

The semicarbazone formed white crystals from 50% methanol, m.p. 128–129°.

Anal. Calc'd for $C_{13}H_{21}N_3O_5S$: C, 47.1; H, 6.4; N, 12.7.
Found: C, 46 7;H, 6.7; N, 12.7.

The toluene filtrate from the insoluble sodium enolate was cooled in an ice-bath and extracted twice with ice-water. The extracts were immediately acidified and extracted with benzene. After being washed with aqueous sodium bicarbonate and water, the solution was evaporated to dryness *in vacuo*. The residue of XII and XIII (R = $-(CH_2)_4COOCH_3$) was a light yellow oil; yield, 3 g. (13%). It gave a transitory purple color with ferric chloride.

Anal. Calc'd for $C_{12}H_{18}O_5S$: C, 52.6; H, 6.5.
Found: C, 52.9; H, 7.1.

Ferric chloride titration of the keto ester fractions. To a solution of 1.03 g. of 2-(δ-carbomethoxybutyl)-4-keto-5-carbomethoxythiophane (XIII) from the insoluble sodium enolate fraction and 2 drops of methyl acetoacetate in 20 cc. of methanol was added 0.37 *N* ferric chloride in 80% methanol until a permanent (one hour) color was obtained. This required 9.8 cc. of the reagent or 97% of that required for oxidation to a double compound. The latter was obtained as an oil on dilution with water.

A solution of 0.90 g. of the keto ester from the soluble sodium enolate fraction was titrated in the same manner and 4.0 cc. of 0.37 *N* ferric chloride taken up in order to obtain a purple color which did not bleach after one hour. This corresponds to 45% of 2-(δ-carbomethoxybutyl)-4-keto-5-carbomethoxythiophane (XIII) and 55% of 2-(δ-carbomethoxy)-3-carbomethoxy-4-ketothiophane (XII). The solution was diluted with several volumes of water and extracted with benzene containing a little ether. The organic layer was cooled in an ice-bath and extracted with iced 3% sodium hydroxide. The aqueous extract was immediately acidified and the keto ester, XII, isolated in the usual manner; yield, 0.19 g It gave a permanent purple color with alcoholic ferric chloride. The semicarbazone formed white crystals from 50% methanol, m.p. 127–129°. A mixture with the semicarbazone of XIII, described above, melted at 102–105°.

Anal. Calc'd for $C_{13}H_{12}N_3O_5S$: N, 12.7. Found: N, 12.5.

2-(δ-Carbomethoxybutyl)-4-cyano-5-carbomethoxydihydrothiophene. To a mixture of 13.7 g of 2-(δ-carbomethoxybutyl)-4-keto-5-carbomethoxythiophane (XIII, from the insoluble sodium enolate) and 5 cc. of hydrogen cyanide cooled in an ice-bath was added 0.05 cc. of 50% potassium hydroxide. After fifteen hours at 0°, the mixture was acidified with 0.15

cc. of 85% phosphoric acid and the volatile material removed *in vacuo*. The residue was dissolved in 25 cc. of benzene, dried with sodium sulfate and the drying agent rinsed with 15 cc. of benzene. The solution, diluted with 40 cc. of reagent pyridine, was treated with 10.6 cc. of phosphorus oxychloride. The temperature was maintained at 40–45° by occasional cooling. After a total of six hours, the mixture was poured on iced hydrochloric acid and extracted with benzene. The extract was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and dilute hydrochloric acid. Distillation gave 10.5 g. (75%) of a yellow oil, b.p. 189–193° (1 mm.).

Anal. Calc'd for $C_{13}H_{17}NO_4S$: N, 4.9. Found: N, 4.9.

2-(δ-Carboxybutyl)thiophane-3,4-trans-dicarboxylic acid. A mixture of 7.2 g. 2-(δ-carbomethoxybutyl)-4-keto-3 and 5-carbomethoxythiophane (XII and XIII obtained from the soluble sodium enolate fraction) was converted to a mixture of 2-(δ-carbomethoxybutyl)-4-cyano-3 and 5-carbomethoxydihydrothiophene as described in the preceding experiment; yield, 5.4 g. (73%) of a yellow oil, b.p. 178–193° (1 mm), but mainly at 183°.

A solution of this mixture in 16 cc. of acetic acid and 27 cc. of concentrated hydrochloric acid was refluxed for seventeen hours, then evaporated to dryness *in vacuo*. The residue was extracted with acetone, filtered from ammonium chloride and again evaporated. The residue consisted of 5.2 g. (100%) of 2-(δ-carboxybutyl)dihydrothiophene-3,4 and 4,5-dicarboxylic acids.

A solution of the 5.2 g. of unsaturated triacids in 23 cc. of 10% sodium hydroxide and 33 cc. of water was stirred with 55 g. of 2% sodium amalgam at 70–80° for two hours. The decanted solution was acidified, saturated with salt and extracted twice with ethyl acetate. Dried with magnesium sulfate, the extracts were evaporated *in vacuo*. The residue was crystallized from 1:3 ethyl acetate-benzene; yield, 1.45 g. (28%) of white crystals, m.p. 105–109° dec.

Recrystallization of a similar preparation from acetone-benzene gave solvated crystals, m.p. 118–120° dec.

Anal. Calc'd for $C_{11}H_{16}O_6S \cdot \frac{1}{2}\,C_3H_6O$: C, 49.7; H, 6.2; S, 10.6; N.E., 102.
Found: C, 49.7; H, 5.7; S, 10.2; N.E., 113.

The material was desolvated by drying at 135° (1 mm.) over phosphorus pentoxide for three hours. An oil formed with gas evolution, and resolidified on cooling, m.p. 124–125°.

Anal. Calc'd for $C_{11}H_{16}O_6S$: C, 47.8; H, 5 8; S, 11.6.
Found: C, 47.4; H, 5.0; S, 11.9.

The filtrate from the 1.45 g of triacid was evaporated to dryness *in vacuo* and heated overnight on the steam-bath with 3.5 g. of sodium hydroxide in 14 cc. of water. The solution was acidified and worked up as described above. In this way an additional 0.51 g. (10%) of white crystals, m.p. 112–115° dec. was obtained.

The trianilide of both fractions was prepared by way of triacid chloride and aniline in the usual manner, white crystals from dilute alcohol, which shrink at 240° and melt at 252°.

Anal. Calc'd for $C_{29}H_{31}N_3O_3S$: C, 69.5; H, 6.2; N, 8.4.
Found: C, 69.5; H, 6.4; N, 8.3.

When 2-(δ-carbomethoxybutyl)-4-cyano-5-carbomethoxydihydrothiophene was hydrolyzed and the product treated with sodium amalgam as described above, no crystalline triacid could be isolated.

SUMMARY

A synthesis of 2-(δ-carboxybutyl)thiophane-3,4-*trans*-dicarboxylic acid has been described.

NEW YORK, N. Y.
PEARL RIVER, N. Y.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

BIOTIN. IV. A SECOND SYNTHESIS OF 2-(δ-CARBOXYBUTYL)-THIOPHANE-3,4-DICARBOXYLIC ACID

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In the previous communication of this series (1) 2-(δ-carboxybutyl)thiophane-3,4-*trans*-dicarboxylic acid (XIV) was synthesized by a method which involved as an intermediate step the Dieckmann cyclization of methyl 3-(carbomethoxymethylthio)suberate. This reaction gave predominately 2-(δ-carbomethoxybutyl)-4-keto-5-carbomethoxythiophane and a low yield of the desired 2-(δ-carbomethoxybutyl)-4-keto-3-carbomethoxythiophane. As a direct result, the over-all yield of the crystalline triacid was too low to afford sufficient material for further transformations.

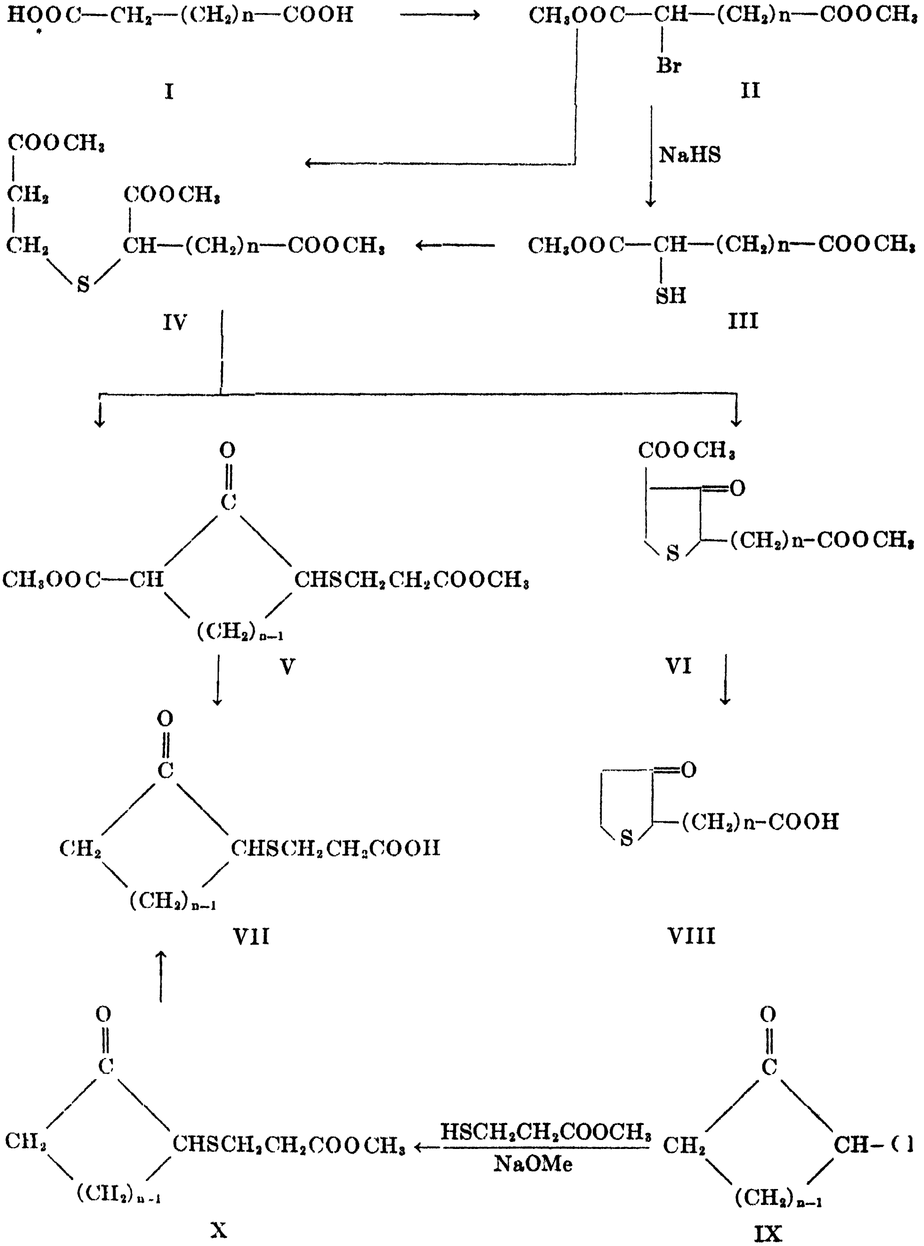
Investigation of a second method of synthesis has now led to a 23% over-all yield of the crystalline *trans* triacid, XIV, in seven steps from pimelic acid.

Staudinger and Ruzicka (2), although they gave no experimental details, prepared α-bromoadipic ester by bromination of adipyl chloride. Despite the statements of v. Braun and Meyer (3), this method has given good results in this laboratory, and the mixture of esters was readily separated by distillation through a Widmer column. Adipic acid gave 50–53% yields of methyl α-bromoadipate and 23–25% of methyl adipate. Pimelic acid gave the same yield of methyl α-bromopimelate and about 30% of methyl pimelate which was reconverted to pimelic acid.

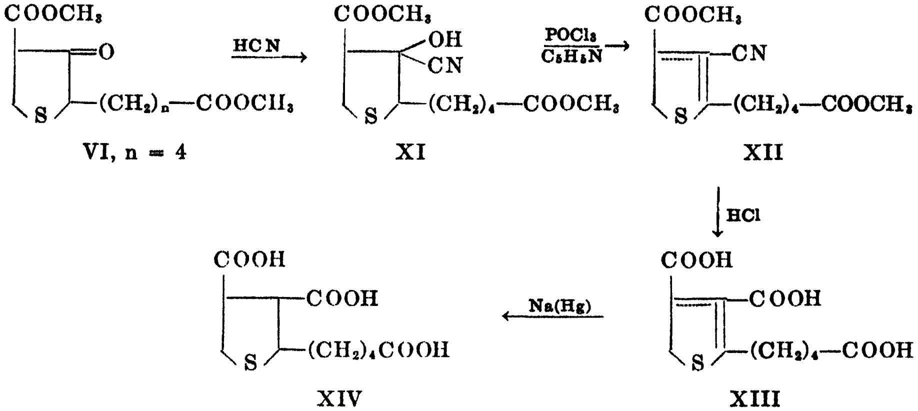
Methyl α-bromoadipate, when treated with sodium hydrosulfide under a variety of conditions, gave as a maximum a 38% yield of methyl α-mercaptoadipate. The latter smoothly added methyl acrylate to give IV (n = 3), which was cyclized by the Dieckmann method. This cyclization can lead to either a cyclopentanone derivative (V, n = 3) or a thiophanone derivative (VI, n = 3) or both. The cyclization was proved to give the latter in the following manner:

Hydrolysis of the keto ester with dilute sulfuric acid gave a crystalline acid, m.p. 73–74° which is either VII or VIII (n = 3). The acid formed a semicarbazone, m.p. 190° dec. The cyclopentanone thioacid, VII, was synthesized by condensing β-mercaptopropionic ester with 2-chlorocyclopentanone followed by acid hydrolysis. The acid, VII, did not crystallize but did give a semicarbazone, m.p. 178–179° dec. A mixture of the two semicarbazones gave a depression in melting point, proving that the keto acid prepared by hydrolysis of the Dieckmann product had structure VIII (n = 3) and its precursor structure, VI (n = 3).

The procedure of Karrer, Keller, and Usteri (4) is excellent for the preparation of methyl α-(carbomethoxyethylthio)pimelate (IV, n = 4). Although these authors ran the Dieckmann cyclization, they did not offer proof as to whether the product was a cyclohexanone derivative (V, n = 4) or a thiophanone derivative (VI, n = 4). This ring closure product has now been established as VI



(n = 4) in the same manner as in the n = 3 series described above.[1] Hydrolysis of the Dieckmann product, according to the method of Karrer, Keller, and Usteri (4), resulted in a keto acid, m.p. 68–69°, which gave a depression in melting point when mixed with an authentic sample of 2-(carboxyethylthio)cyclohexanone (VII, n = 4), m.p. 82–83°. A mixture of the semicarbazones also gave a depression in melting point.



Treatment of 2-(δ-carbomethoxybutyl)-3-keto-4-carbomethoxythiophane (VI, n = 4) with liquid hydrogen cyanide resulted in the formation of cyanohydrin, XI, which was dehydrated with phosphorus oxychloride and pyridine in benzene to 2-(δ-carbomethoxybutyl)-3-cyano-4-carbomethoxydihydrothiophene (XII). Acid hydrolysis gave the unsaturated triacid, XIII, which was smoothly reduced with sodium amalgam to 2-(δ-carboxybutyl)thiophane-3,4-dicarboxylic acid (XIV). The *trans* isomer (1) readily crystallized from a mixture of ethyl acetate and benzene in 45–50% yield. The non-crystalline isomers in the filtrate were esterified, treated with sodium methoxide and hydrolyzed. By inversion in this manner an additional 20–25% of the same crystalline *trans* isomer was obtained. The inversion was also carried out by heating a solution of the triacid filtrates with aqueous alkali.

Acknowledgment. The authors wish to thank Messrs Louis Brancone, Philip Weiss, and Miss Barbara Eames for the microanalyses.

EXPERIMENTAL

Methyl α-bromopimelate. A mixture of 252 g. of pimelic acid, 250 cc. of chloroform, and 250 cc. of thionyl chloride was refluxed for forty minutes, solution being complete in twenty minutes. After the addition of 86 cc. of bromine, the mixture was refluxed until the bromine had reacted which required two to three hours. The stirred or shaken mixture was then treated dropwise cautiously with 300 cc. of methanol at such a rate that the solution refluxed briskly. After being refluxed fifteen minutes more, the solution was washed with water and the solvent removed *in vacuo*. The residue, distilled through a Widmer column gave a forerun of 91 g. (31%) of methyl pimelate, b.p. 100–102° (1 mm.) followed by 219 g.

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[1] After this work was completed, Cheney and Piening (5) proved the mode of ring closure of IV (n = 4) by another method.

(52%, or 77% based on the methyl pimelate not recovered) of methyl α-bromopimelate, b.p. 122–126° (1 mm.).

Anal. Calc'd for $C_{19}H_{15}BrO_4$: C, 40.3; H, 5.6.
Found: C, 39.9; H, 5.3.

Methyl α-bromoadipate was prepared in the same manner in about the same yields, b.p. 148–151° (14 mm.). The formation of the acid chloride required two hours.

Methyl α-mercaptoadipate. To a solution of 12 g. of potassium hydroxide in 60 cc. of methanol saturated with hydrogen sulfide at 0° was added 26.5 g. of methyl α-bromoadipate. Heat was evolved and potassium bromide separated. The mixture was refluxed for thirty minutes, then acidified with acetic acid and diluted to 500 cc. with water. The oil was extracted with benzene and distilled, b.p. 154–157° (18 mm.); yield, 8.4 g. (38%). There was a large residue of thio ether.

For analysis 5 g. of a similar preparation was dissolved in ether and extracted with cold 3% sodium hydroxide. After acidification the oil was extracted with benzene, washed with sodium bicarbonate solution, and redistilled, colorless liquid, b.p. 153° (18 mm.).

Anal. Calc'd for $C_8H_{14}O_4S$: C, 46.7; H, 6.8.
Found: C, 47.1; H, 6.2.

If the reaction was run at 0–3° for twenty-four hours the yield was 32%. When the same reaction was run by dropwise addition of the bromo ester with stirring at 20–25° (thirty minutes) while a continuous stream of hydrogen sulfide was led through the solution, then allowed to stand at room temperature for eighteen hours, the yield was 27%. Substitution of sodium for the potassium hydroxide gave a 38% yield if boiled three hours or 33% if allowed to stand at room temperature for thirteen hours, then refluxed ninety minutes.

2-(γ-Carboxypropyl)-3-ketothiophane (VIII, n = 3). To a mixture of 14.7 g. of α-mercaptoadipic ester and 8.5 cc. of acrylic ester cooled in an ice-bath was added 0.15 cc. of piperidine. The temperature rose to 70°. After standing overnight at room temperature, the oil was dissolved in 100 cc. of dry ether and added in a nitrogen atmosphere to the dry sodium ethoxide from 2 g. of sodium, obtained by evaporating its ethanolic solution to dryness *in vacuo*. After twenty hours the clear solution was poured into iced water, the aqueous layer separated and acidified. The oil was extracted with benzene, washed twice with aqueous sodium bicarbonate, then water. Evaporation *in vacuo* gave 14.5 g. (77%) of VI (n = 3).

This ester was decarbethoxylated by refluxing with 150 cc. of 10% sulfuric acid for four hours. The clear solution was saturated with salt and extracted twice with ethyl acetate. The extracts were washed twice with saturated salt solution, then evaporated. The residue was crystallized from carbon tetrachloride; yield, 8.5 g. (83%), m.p. 73–74°. For analysis a sample was recrystallized from the same solvent, white crystals, m.p. 73–74°.

Anal Calc'd for $C_8H_{12}O_3S$: C, 51.1; H, 6.4; N.E., 188.
Found: C, 50.8; H, 5.7; N.E., 180.

The semicarbazone formed white crystals from 50% aqueous Cellosolve, m.p. 190° dec.

Anal. Calc'd for $C_9H_{15}N_3O_3S$: C, 44.2; H, 6.2.
Found: C, 44.5; H, 6.0.

2-(Carboxyethylthio)cyclopentanone (VII, n = 3) semicarbazone. To a solution of 2.5 g. of sodium in 50 cc. of methanol was added 14 g. of ethyl β-mercaptopropionate followed by 12 g. of 2-chlorocyclopentanone in 30 cc. of methanol in portions with cooling so that the temperature was 10–15°. After fifteen hours at 3°, the mixture was diluted with 150 cc. of water containing 30 cc. of concentrated sulfuric acid. Refluxed for four hours, the mixture was diluted to 500 cc. with water and washed with benzene. The aqueous layer was saturated with ammonium sulfate, then extracted with two 200-cc. portions of ethyl acetate. The extracts, dried with magnesium sulfate and clarified with Norit, were evaporated to dryness *in vacuo* leaving 7 g. of an oil

One gram of the oil in 15 cc. of 50% alcohol was treated with 0.5 g. of anhydrous sodium acetate and 0.5 g. of semicarbazide hydrochloride. After several days the semicarbazone was removed by filtration, m.p. 174–176° dec.; yield, 0.55 g. Recrystallization from 50% alcohol gave white crystals, m.p. 178–179° dec.

Anal. Calc'd for $C_9H_{15}N_3O_3S$: C, 44.2; H, 6.2; N, 17.1.
Found: C, 44.4; H, 6.1; N, 16.7.

A mixture with the semicarbazone of 2-(γ-carboxypropyl)-3-ketothiophane depressed the m.p.

β-Mercaptopropionic acid. A mixture of 100 g. of β-bromopropionic acid (Dow), 50 g. of thiourea, and 200 cc. of water was heated on the steam-bath for seventy-five minutes. After the addition of 78 g. of sodium hydroxide in 390 cc. of water, the solution was again heated on the steam-bath for two hours, then acidified and saturated with salt. The mixture was extracted with three 150-cc. portions of ethyl acetate. The extracts were concentrated *in vacuo* and the residue distilled, b.p. 117–122° (13 mm.), m.p. 17.5°; yield, 50.7 g. (72%).

Runs of five times this size have given the same results. The use of aqueous sodium hydrosulfide instead of thiourea gave the same yield.

Biilman (6) has recorded the b.p. as 110.5–111.5° (15 mm.) and m.p. 16.8°. After this work was completed Cheney and Piening (5) described a similar, though more complicated procedure for the preparation of β-mercaptopropionic acid.

Methyl β-mercaptopropionate. A mixture of 50.7 g. of β-mercaptopropionic acid, 1.5 cc. of concentrated sulfuric acid, 150 cc. of chloroform, and 100 cc. of methanol was refluxed for sixteen hours under a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. After being washed with 400 cc. of water, the mixture was distilled through a Vigreux column at atmospheric pressure to remove solvent. Distillation of the residue gave 53.6 g. (94%) of a water-white liquid, b.p. 64–65° (13 mm.).

Methyl α-(carbomethoxyethylthio)pimelate (IV, n = 4). By condensation of 43 g. of methyl β-mercaptopropionate with 81 g. of methyl α-bromopimelate in methanol containing sodium methoxide at −20° followed by eight hours at room temperature essentially by the method of Karrer, Keller, and Usteri (4), there was obtained 82 g. (88%) of product, b.p. 192–195° (1 mm.). The b.p. varies considerably with the bath temperature and rate of distillation.

Anal. Calc'd for $C_{13}H_{22}O_6S$: C, 50.9; H, 7.3.
Found: C, 51.0; H, 7.7.

In other runs much larger than the above the yield was 85–88%.

2-(Carbomethoxybutyl)-3-keto-4-carbomethoxythiophane (VI, n = 4). To a suspension of 33 g. of sodium methoxide (Mathieson) in 500 cc. of benzene was added 135 g. of methyl α-(carbomethoxyethylthio)pimelate (IV, n = 4) in 100 cc. of benzene. After eighteen hours at room temperature protected from moisture, the solution was poured into iced water, diluted with a little ether and the aqueous layer separated. The organic layer was extracted once more with ice-water and the aqueous extracts were immediately acidified. (In some runs the crystalline sodium enolate separated when the benzene solution was extracted with ice-water. This redissolved on adding sufficient water.) The separated oil was extracted with benzene, washed with aqueous sodium bicarbonate, then water. Evaporation of the solvent *in vacuo* left 96.4 g. (80%) of a yellow oil. In other runs the yields were 75–80%.

Anal. Calc'd for $C_{12}H_{18}O_5S$: C, 52.6; H, 6.6.
Found: C, 52.5; H, 6.5.

2-(δ-Carboxybutyl)-3-ketothiophane (VIII, n = 4). From 8.7 g. of 2-(δ-carbomethoxybutyl)-3-keto-4-carbomethoxythiophane (VI, n = 4), 10 cc. of acetic acid, 5 cc. of concentrated sulfuric acid, and 35 cc. of water was obtained 4.8 g. (71%) of product, m.p. 64–67°, essentially by the method of Karrer, Keller, and Usteri (4). Recrystallization from benzene-petroleum ether raised the m.p. to 68–69°.

Anal. Calc'd for $C_9H_{14}O_3S$: C, 53.3; H, 6.9.
Found: C, 53.0; H, 6.3.

Karrer, Keller, and Usteri (4) give the m.p. as 68°.

The semicarbazone formed white crystals from dilute methanol, m.p. 175–176°.

Anal. Calc'd for $C_{10}H_{17}N_3O_3S$: C, 46.3; H, 6.6; N, 16.2.
Found: C, 46.2; H, 6.7; N, 16.5.

2-(Carbomethoxyethylthio)cyclohexanone (X, n = 4). To a solution of 8.7 g. of sodium methoxide (Mathieson) in 75 cc. of methanol was added 20.5 g. of β-mercaptopropionic ester in 25 cc. of methanol. To the stirred solution was added 21 g. of 2-chlorocyclohexanone in 40 cc. of methanol over a period of twenty-five minutes maintaining the temperature at −20°. After being stirred for fifty minutes at room temperature, the mixture was diluted with 500 cc. of water, extracted with benzene and the extract washed successively with aqueous sodium bicarbonate and dilute hydrochloric acid. Distillation gave 23.6 g. (64%) of a colorless oil, b.p. 132° (1 mm.).

Anal. Calc'd for $C_{10}H_{16}O_3S$: C, 55.6; H, 7.5.
Found: C, 55.8; H, 7.7.

2-(Carboxyethylthio)cyclohexanone (VII, n = 4). A mixture of 1 g. of 2-(carbomethoxyethylthio)cyclohexanone, 2 cc. of acetic acid, 7 cc. of water, and 1 cc. of concentrated sulfuric acid was refluxed for three hours, diluted with water, and extracted with ethyl acetate. The extract was dried with magnesium sulfate and the resultant oil obtained on evaporation was crystallized from benzene-petroleum ether; yield, 0.61 g. (65%), m.p. 75–77°. Recrystallization from carbon tetrachloride with the aid of Norit gave white crystals, m.p. 82–83°.

Anal. Calc'd for $C_9H_{14}O_3S$: C, 53.3; H, 6.9.
Found: C, 52.8; H, 7.2.

A mixed m.p. with 2-(δ-carboxybutyl)-3-ketothiophane (VIII, n = 4) was 43–47°.

The semicarbazone prepared in and recrystallized from dilute methanol, formed white crystals, m.p. 163–164°. On admixture with the semicarbazone of 2-(δ-carboxybutyl)-3-ketothiophane a depression in m.p. was observed.

Anal. Calc'd for $C_{10}H_{17}N_3O_3S$: C, 46.3; H, 6.6; N, 16.2.
Found: C, 46.7; H, 6.8; N, 16.3.

The 2-(carboxyethylthio)cyclohexanone, after standing for two years, became tan colored and melted at 113–116°.

2-(δ-Carbomethoxybutyl)-3-hydroxy-3-cyano-4-carbomethoxythiophane (XI). To a mixture of 55 g. of 2-(δ-carbomethoxybutyl)-3-keto-4-carbomethoxythiophane (VI) and 20 cc. of liquid hydrogen cyanide at 0° was added 0.3 cc. of 50% potassium hydroxide. After sixteen hours at 0°, the mixture was acidified with 1 cc. of 85% phosphoric acid and the volatile material removed *in vacuo* on the steam-bath; yield, 63 g. (quant.) of a nearly colorless oil which partially crystallized on standing.

Anal. Calc'd for $C_{13}H_{19}NO_5S$: N, 4.6. Found: N, 4.6.

2-(δ-Carbomethoxybutyl)-3-cyano-4-carbomethoxydihydrothiophene (XII). A solution of 62.5 g. of the above cyanohydrin (XI) in 100 cc. of benzene was dried with sodium sulfate and the drying agent rinsed with 50 cc. of benzene. To the solution, diluted with 150 cc. of reagent pyridine was added 43 cc. of phosphorus oxychloride. The temperature gradually rose to 40° and was occasionally cooled to maintain the temperature at 40–48°. In thirty minutes the heat of reaction started to subside. After a total of six hours, the mixture was poured on ice. The separated organic layer, washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate, and dilute hydrochloric acid, was then distilled. The product was a yellow oil, b.p. 192–198° (1 mm.); yield, 41 g. (70%).

Anal. Calc'd for $C_{13}H_{17}NO_4S$: C, 55.2; H, 6.0; N, 4.9.
Found: C, 55.5; H, 6.0; N, 5.4.

2-(δ-Carboxybutyl)dihydrothiophene-3,4-dicarboxylic acid (XIII). A solution of 29.2 g. of 2-(δ-carbomethoxybutyl)-3-cyano-4-carbomethoxydihydrothiophene (XII) in 90 cc. of acetic acid and 150 cc. of concentrated hydrochloric acid was refluxed for sixteen hours, then evaporated to dryness *in vacuo*. The residue was extracted with 300 cc. of hot acetone, filtered from ammonium chloride (5.1 g.) and the extract evaporated to dryness *in vacuo*. Most of the residue solidified on standing; yield 28.9 g. (quant.).

Anal. Calc'd for $C_{11}H_{14}O_6S$: C, 48.2; H, 5.1.
Found: C, 47.4; H, 5.3.

The above material is sufficiently pure for the next step. It is difficult to recrystallize as it readily solvates. However, 90% of it can be obtained crystalline from ethyl acetate-benzene in three crops, m.p. between 110–120° dec. Several more recrystallizations of a sample from the same solvents gave white crystals which were still solvated, m.p. 127–129°.

Anal. Found: C, 52.2; H, 5.2.

2-(δ-Carboxybutyl)thiophane-3,4-trans-dicarboxylic acid (*XIV*). A solution of 23.5 g. of 2-(δ-carboxybutyl)dihydrothiophene-3,4-dicarboxylic acid (XIII) in 106 cc. of 10% sodium hydroxide and 140 cc. of water was stirred with 265 g. of 2% sodium amalgam at 70–80° (bath temp.) for one hour. The decanted solution was acidified, saturated with salt, and extracted with two 250-cc. portions of ethyl acetate. The extracts, dried with magnesium sulfate, were evaporated to dryness and the semi-crystalline residue (22.5 g.) recrystallized from 1:4 ethyl acetate-benzene, white crystals, m.p. 103–112° dec.; yield 11.4 g. (49%).

This acid contains benzene of crystallization and is suitable for the next step. It can be purified by recrystallization from ethyl acetate, m.p. 123°. A mixture with this same acid prepared by a different method (1) gave no depression in m.p.

Anal. Calc'd for $C_{11}H_{16}O_6S$: C, 47.8; H, 5.9

Found: C, 47.8, 47.4; H, 6.6, 6.4.

The trianilide, prepared as previously described (1), shrinks at 242° and melts at 254°, and gave no depression in m.p. when mixed with the earlier preparation.

The material in the filtrates from the triacid (XIV) from reduction of 61 g. of 2-(δ-carboxybutyl)dihydrothiophene-3,4-dicarboxylic acid (XIII) was esterified with methanol, chloroform, sulfuric acid, and magnesium sulfate in a Soxhlet in the usual manner. The crude *cis* trimethyl esters were converted to *trans* by boiling in methanol containing sodium methoxide for two hours. Hydrolysis gave an additional 14.5 g. (24%) of *trans* triacid (XIV), m.p. 111–115° identical with the material obtained by direct crystallization of the reduction mixture.

The trianilide was identical with that described above.

The inversion may also be carried out by heating for five hours on the steam bath the non-crystalline acids in the filtrate with an equal weight of sodium hydroxide in three parts of water.

SUMMARY

2-(δ-Carboxybutyl)thiophane-3,4-*trans*-dicarboxylic acid has been synthesized in good yield by a seven-step process starting with pimelic acid.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

BIOTIN. V. *cis*-3,4-DIAMINOTHIOPHANE

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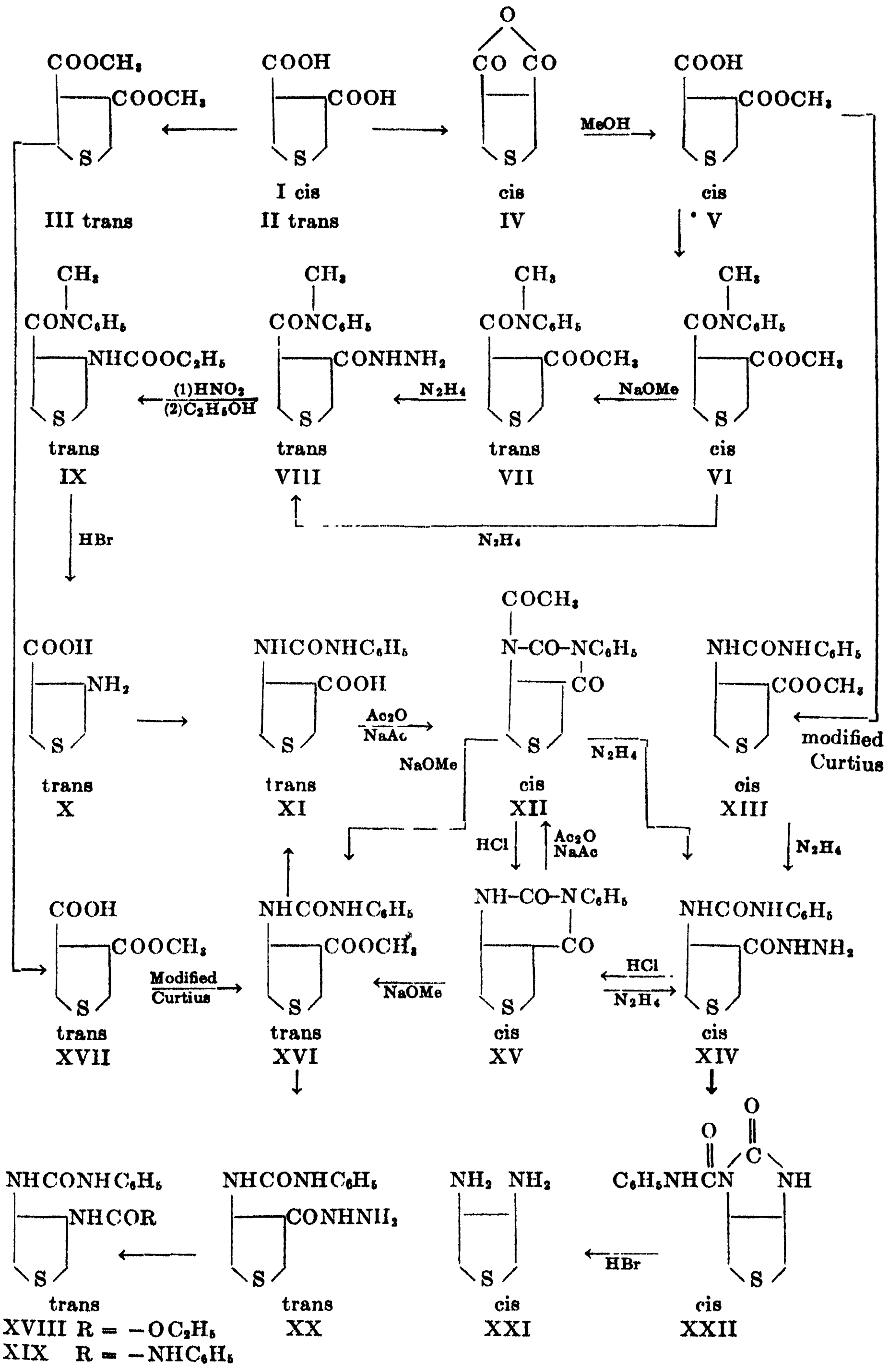
Previous communications in this series (1, 2) have shown that treatment of 2-alkylthiophane-3,4-*cis*-dicarboxylic acid esters with hydrazine caused inversion of configuration to take place with the formation of 2-alkylthiophane-3,4-*trans*-dicarboxhydrazides. As other methods of degrading both *cis*-carboxyls simultaneously to *cis*-diamines also failed, it became apparent that the carboxyl groups would have to be degraded one at a time. Investigation of the stepwise degradation of thiophane-3,4-dicarboxylic acid has now led to two methods of synthesizing *cis*-4-uranilinothiophane-3-carboxhydrazide (XIV) which in turn could be further degraded to *cis*-3,4-diaminothiophane.

Thiophane-3,4-*cis*-dicarboxylic anhydride (IV), when refluxed with methanol, gave a crystalline monomethyl ester (V), which was converted to the *cis*-methylanilide, VI, *via* the acid chloride. Heated with hydrazine, the *cis*-4-(N-methylcarbanilido)-3-carbomethoxythiophane (VI) failed to give the desired *cis* hydrazide corresponding to VIII. Instead a mixture of *trans*-4-(N-methylcarbanilido)thiophane-3-carboxhydrazide (VIII) in about 35% yield along with lesser amounts of thiophane-3,4-*trans*-dicarboxhydrazide and thiophane-3,4-*cis*-dicarboxy-N,N′-cyclic hydrazide were formed. The configuration of VIII was established as *trans* in two ways. Acid hydrolysis resulted in *trans*-4-(N-methylcarbanilido)thiophane-3-carboxylic acid which was identical with a sample synthesized by treating the diacid chloride of thiophane-3,4-*trans*-dicarboxylic acid (II) with a limited amount of methylaniline. The second proof consisted of treating the *cis* ester anilide, VI, with methanolic sodium methoxide, causing inversion to the isomeric *trans* ester, VII, in 90% yield. The latter smoothly reacted with hydrazine with formation of *trans*-4-(N-methylcarbanilido)thiophane-3-carboxhydrazide (VIII), identical with that obtained from *cis* ester anilide, VI.

Although this method failed to give a *cis* hydrazide, the Curtius degradation was carried out in order to have reference compounds of the *trans* series. The so obtained *trans*-3-carbethoxyamino-4-(N-methylcarbanilido)thiophane (IX) was hydrolyzed with hydrobromic acid to *trans*-3-aminothiophane-4-carboxylic acid (X), characterized as its benzoyl and phenylurea (XI) derivatives.

When the acid chloride of thiophane-3,4-*cis*-dicarboxylic acid monomethyl ester (V) was treated with sodium azide and the resulting azide rearranged to *cis*-3-carbomethoxy-4-carbomethoxyaminothiophane, the latter could not be crystallized. Hydrobromic acid hydrolysis of the crude product followed by benzoylation gave *cis*-4-benzoylaminothiophane-3-carboxylic acid, isomeric with the *trans* acid described above. However, when the azide was rearranged and the isocyanate treated with aniline, crystalline *cis*-3-carbomethoxy-4-uranilino-

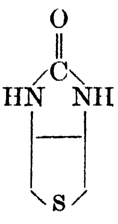

III trans
I cis
II trans
cis
IV
MeOH
cis
V
trans
IX
(1)HNO₂
(2)C₂H₅OH
trans
VIII
N₂H₄
trans
VII
NaOMe
cis
VI
N₂H₄
HBr
trans
X
trans
XI
Ac₂O
NaAc
NaOMe
cis
XII
N₂H₄
cis
XIII
modified Curtius
N₂H₄
HCl
Ac₂O
NaAc
trans
XVII
Modified Curtius
trans
XVI
NaOMe
cis
XV
HCl
N₂H₄
cis
XIV
trans
XVIII R = –OC₂H₅
XIX R = –NHC₆H₅
trans
XX
cis
XXI
HBr
cis
XXII

thiophane (XIII) was isolated. This was readily converted to *cis*-4-uranilinothiophane-3-carboxhydrazide (XIV) with hydrazine. That this was a *cis* hydrazide was demonstrated by the following procedure:

trans-3,4-Dicarbomethoxythiophane (III) was hydrolyzed with one equivalent of alkali in good yield to the oily monomethyl ester, XVII. This was characterized by conversion to its N-methylanilide, identical with VII prepared as shown on the flow sheet. The monoester, XVII, was degraded *via* the acid chloride with sodium azide to *trans*-4-uranilino-3-carbomethoxythiophane (XVI), isomeric to the corresponding *cis* urea derivative, XIII. The ester, XVI, was converted to the *trans* hydrazide, XX. Although the *cis* hydrazide, XIV, and the *trans* hydrazide, XX, melted about 30° apart, mixtures did not give significant depressions. However, Curtius degradation readily distinguished them. The *cis* hydrazide, XIV, gave an isocyanate which readily cyclized to 4-carbanilido-5-ketoimidazolido[4,5,c,*cis*]thiophane (XXII), when the azide was boiled in chloroform. The *trans* hydrazide, XX, under the same conditions gave an isocyanate which would not cyclize and was characterized as the urethan, XVIII, or uranilino derivative, XIX.

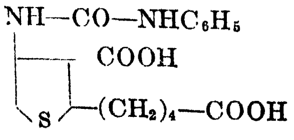
The imidazolone, XXII, was slowly hydrolyzed with 48% hydrobromic acid to 3,4-*cis*-diaminothiophane (XXI) which was isolated as the dihydrobromide and the insoluble dipicrate. It was characterized as its dibenzoyl derivative, m.p. 230-231°, which was isomeric with *trans*-3,4-dibenzoylaminothiophane, m.p. 295-300° (3). It was identical with the dibenzoate of "isomer B" of 3,4-diaminothiophane, m.p. 238-239°, described by Kilmer and McKennis (4).

The *cis* and *trans* diamines were distinguished by another method. Treatment of the *trans*-diamine hydrobromide with phosgene at 0° in excess aqueous sodium bicarbonate resulted in no reaction, as the highly insoluble dipicrate of the diamine could be recovered quantitatively. However, when the *cis*-diamine dihydrobromide was treated under the same conditions, none of the highly insoluble dipicrate formed, indicating that a reaction had taken place. The cyclic urea derivative, XXIII, m.p. 231° was isolated.

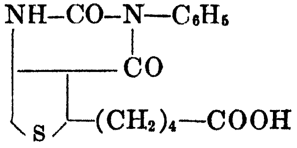


cis

XXIII



XXIV



XXV

In a subsequent communication (7) a synthesis of 2-(δ-carboxybutyl)-4-uranilinothiophane-3-*trans*-carboxylic acid (XXIV) will be described. In this molecule it was necessary to degrade the ring carboxyl to an amine and leave the side chain carboxyl intact in order to obtain a 2-(δ-carboxybutyl)-3,4-diaminothiophane. One of the possible ways of distinguishing between the carboxyl groups would be the formation of a uracil, XXV. For preliminary studies, the preparation and reactions of the model uracil, XV, was undertaken in order to avoid the complications caused by a side chain.

When *cis*-4-uranilinothiophane-3-carboxhydrazide (XIV) was heated with dilute hydrochloric acid, ring closure (6) to the insoluble 3-phenyl-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (XV) took place. In contrast, the corresponding *trans* hydrazide (XX) was merely hydrolyzed to *trans*-4-uranilinothiophane-3-carboxylic acid (XI). This gives a second method of distinguishing between the *cis* and *trans* hydrazides, as the *cis* configuration is necessary for ring closure to take place under these conditions.

Although the ring of dihydrouracils has been reported (5) to be difficultly opened, the thienouracil, XV, opened with extreme ease. The configuration obtained depended upon the reaction conditions. With hydrazine at 100° for ten minutes, the ring of XV opened to give a 92% yield of *cis*-4-uranilinothiophane-3-carboxhydrazide (XIV). The configuration was determined as *cis* by reclosure to XV. If the reaction was run with a larger excess of hydrazine and heated for two hours on the steam-bath, mainly the *trans* hydrazide was obtained. When XV was boiled for five minutes with methanolic sodium methoxide, the ring was rapidly ruptured with the formation of *trans*-3-carbomethoxy-4-uranilinothiophane (XVI), identical with an authentic sample described previously.

As hydrochloric acid treatment of *trans*-4-uranilinothiophane-3-carboxylic acid (XI) failed to cause ring closure, in contrast to the *cis* series, the use of boiling propionic or acetic anhydrides (6) was tried. This method appeared to give small yields of the impure uracil. However, when sodium acetate was introduced into the reaction mixture to promote enolization, inversion and ring closure took place in ten minutes to give a 69% yield of 1-acetyl-3-phenyl-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (XII). The structure and configuration of this compound was demonstrated by acid hydrolysis to the *cis* uracil, XV, and its reformation by acetylation. The acetyl uracil, XII, reacted with hydrazine or sodium methoxide in methanol with the same ease as the non-acetylated uracil, XV, losing the acetyl group with the formation of *cis*-4-uranilinothiophane-3-carboxhydrazide (XIV) and *trans*-3-carbomethoxy-4-uranilinothiophane (XVI), respectively.

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EXPERIMENTAL

Thiophane-3,4-cis-dicarboxylic anhydride (IV). A solution of 16.5 g. of *cis* and *trans*-thiophane-3,4-dicarboxylic acid (m.p. 100–120°) in 85 cc. of propionic anhydride was refluxed for three hours. Distillation gave 12.8 g. (87%) of anhydride, b.p. 145–148° (1 mm.), m.p. 79–82° (2).

Thiophane-3,4-cis-dicarboxylic acid monomethyl ester (V). A mixture of 11 g. of thiophane-3,4-*cis*-dicarboxylic anhydride (IV) and 40 cc. of methanol was refluxed for ninety minutes, then solvent removed *in vacuo.* The residue was recrystallized from benzene-petroleum ether, white crystals, m.p. 107–109°; yield, 10 g. (76%). Recrystallization of a sample from benzene raised the m.p. to 107.5–109°.

Anal. Calc'd for $C_7H_{10}O_4S$: C, 44.2; H, 5.3.
Found: C, 44.4; H, 5.8.

The corresponding ethyl ester was prepared in the same manner, but was difficult to crystallize: white crystals, m.p. 55–59°; yield, 41%.

Anal. Calc'd for $C_8H_{12}O_4S$: C, 47.2; H, 5.9.
Found: C, 47.5; H, 5.8.

cis-4-Carbanilidothiophane-3-carboxylic acid. To a warm solution of 200 mg. of thiophane-3,4-*cis*-dicarboxylic anhydride (IV) in 5 cc. of benzene was added 0.2 cc. of aniline. The anilic acid immediately crystallized and was collected on a filter; yield, 310 mg. (98%) of white crystals, m.p. 140–142°.

Anal. Calc'd for $C_{12}H_{13}NO_3S$: C, 57.3; H, 5.2; N, 5.6.
Found: C, 57.1; H, 5.0; N, 5.9.

N-Phenylthiophane-3,4-cis-dicarboximide. (*A*). A solution of 200 mg. of thiophane-3,4-*cis*-dicarboxylic acid monomethyl ester (V) and 0.2 cc. of thionyl chloride in 5 cc. of benzene was refluxed for thirty minutes, then evaporated *in vacuo.* The residue in 10 cc. of benzene was treated with 0.4 cc. of aniline and heated on the steam-bath for two minutes. The mixture was diluted with 10 cc. of ethyl acetate, washed twice with dilute hydrochloric acid, dilute sodium bicarbonate solution, and water. Evaporation to dryness and trituration with petroleum ether gave 265 mg. (95%) of impure *cis*-4-carbanilido-3-carbomethoxythiophane, m.p. 122–127°. Recrystallization from dilute methanol gave white crystals of N-phenylthiophane-3,4-*cis*-dicarboximide, m.p. 146–147°. A mixture with the 122–127° material melted at 98–110°.

Anal. Calc'd for $C_{12}H_{11}NO_2S$: C, 61.8; H, 4.8; N, 6.0.
Found: C, 61.9; H, 4.8; N, 6.4.

Due to the ease of ring closure it was necessary to use the N-methylanilide instead of the anilide for further transformations.

(*B*) A mixture of 220 mg. of *cis*-3-carbanilidothiophane-4-carboxylic acid and 5 cc. of acetyl chloride was refluxed for ten minutes, then the excess reagent was evaporated. The residue was recrystallized from dilute methanol; yield, 140 mg. (68%) of white crystals, m.p. 143–146° and identical with preparation *A*. The ring closure can also be carried out merely by heating a solution of the acid in 20% aqueous methanol.

cis-4-(N-Methylcarbanilido)thiophane-3-carboxylic acid. To a hot solution of 1.0 g. of thiophane-3,4-*cis*-dicarboxylic anhydride (IV), in 10 cc. of benzene was added 1 cc. of methylaniline. Scratching the wall of the flask caused immediate separation of the product; yield, 1.45 g. (87%), m.p. 160–162°. For analysis a sample was recrystallized from benzene, white crystals, m.p. 161–162°.

Anal. Calc'd for $C_{13}H_{15}NO_3S$: N, 5.3. Found: N, 5.3.

cis-4-(N-Methylcarbanilido)-3-carbomethoxythiophane (VI). (*A*). To a suspension of 1.45 g. of *cis*-4-(N-methylcarbanilido)thiophane-3-carboxylic acid in ether was added an excess of ethereal diazomethane. The acid dissolved with nitrogen evolution in about ten minutes. Evaporation of the solvent and trituration with petroleum ether gave 1.40 g. (92%) of product, m.p. 106–107.5°. Recrystallization from benzene-petroleum ether gave white crystals, m.p. 107–107.5°.

Anal. Calc'd for $C_{14}H_{17}NO_3S$: C, 60.2; H, 6.1; N, 5.0.
Found: C, 59.8; H, 6.3; N, 5.4.

(*B*). A mixture of 5 g. of thiophane-3,4-*cis*-dicarboxylic acid monomethyl ester (V), 5 cc. of thionyl chloride, and 10 cc. of benzene was refluxed for thirty minutes, then evaporated to dryness *in vacuo* (bath 50°). The residue, dissolved in 50 cc. of benzene, was treated with 8.5 cc. of methylaniline and refluxed five minutes. Diluted with 50 cc. of ethyl acetate, the mixture was washed twice with dilute hydrochloric acid, then aqueous sodium bicarbonate, and finally with water. Evaporation *in vacuo* and trituration with petroleum ether gave 6.9 g. (95%) of product, m.p. 106–107°. A mixed m.p. with preparation *A* was the same.

Thiophane-3,4-cis-dicarboxy-N,N′-cyclic hydrazide. A mixture of 340 mg. of (IV), 0.3 cc. of 100% hydrazine hydrate, and 1.0 cc. of water was warmed until homogeneous (one minute). The solution, diluted with 5 cc. of water and acidified with acetic acid, was heated on the steam-bath for ten minutes, then continuously extracted with ethyl acetate for three hours. The extract was evaporated to dryness *in vacuo* and the crystalline residue triturated with petroleum ether; yield 320 mg. (87%), m.p. 126–131°. Several crystallizations from alcohol gave blunt white needles, m.p. 135–135.5°.

Anal. Calc'd for $C_6H_8N_2O_2S$: N, 16.3. Found: N, 16.1.

trans-4-(N-Methylcarbanilido)-3-carbomethoxythiophane (VII). A solution of 5 g. of the corresponding *cis* isomer, (VI), in 25 cc. of methanol containing 0.62 g. of sodium was refluxed for two and one-half hours, cooled, and poured into excess cold dilute hydrochloric acid. The product was washed with water; yield, 4.6 g. (92%), m.p. 120–124°. Recrystallization from benzene-petroleum ether gave white crystals, m.p. 124–126°.

Anal. Calc'd for $C_{14}H_{17}NO_3S$: C, 60.2; H, 6.1; N, 5.0.
Found: C, 60.0; H, 6.0; N, 5.2.

On standing, the aqueous filtrate deposited 54 mg. of white crystals, m.p. 188–190°. A mixed m.p. identified it as *trans*-4-(N-methylcarbanilido)thiophane-3-carboxylic acid, described later.

trans-4-(N-Methylcarbanilido)thiophane-3-carboxhydrazide (VIII). (*A*). A mixture of 4.7 g. of *cis*-(4-N-methylcarbanilido)-3-carbomethoxythiophane (VI) and 1.5 cc. of 100% hydrazine hydrate was refluxed in an oil-bath at 140° for one hour. The mixture was extracted with three 30-cc. portions of hot water, decanting from the oil each time. On cooling, the oil crystallized and consisted of 0.6 g. (13%) of starting material, m.p. 101–103°.

The aqueous extracts, after several hours at 3°, deposited crude VIII, m.p. 150–170°; yield, 1.5 g. (34%). The aqueous filtrate was concentrated to about 15 cc. and after five hours at 3° a second crop of 0.2 g. (4%), m.p. 155–170°, was collected. Recrystallization of a similar preparation several times from water gave white crystals, m.p. 176–178°, which were readily soluble in 1 *N* hydrochloric acid.

Anal. Calc'd for $C_{13}H_{17}N_3O_2S$: C, 55.8; H, 6.1; N, 15.0.
Found: C, 55.5; H, 5.8; N, 14.7.

The aqueous filtrate from the 0.2 g. of *trans* hydrazide on standing overnight at 3°, deposited 0.4 g. (14%) of crude thiophane-3,4-*cis*-dicarboxy-N,N′-cyclic hydrazide, m.p. 120–130°. A mixed m.p. with an authentic sample was 125–132°.

The filtrate from the cyclic hydrazide was evaporated to dryness and the residue dissolved in boiling alcohol. After several hours at room temperature, 0.25 g. (7%) of thiophane-3,4-*trans*-dicarboxhydrazide (3) was obtained, m p. and mixed m.p. 215–217°.

The alcohol filtrate, after standing overnight at −5°, deposited 0.42 g. (15%) of the *cis*-cyclic hydrazide, m.p. 120–130°. Thus, 90% of the reaction products was accounted for and no *cis*-4-(N-methylcarbanilido)thiophane-3-carboxhydrazide could be found.

(*B*). A mixture of 4 g. of *trans*-3-carbomethoxy-4-(N-methylcarbanilido)thiophane (VII) and 2 cc. of 100% hydrazine hydrate was refluxed in an oil-bath at 140° for one hour. The excess reagent was removed *in vacuo* and the solid residue triturated with water; yield, 3.6 g. (90%), m.p. 174–176° and identical with preparation *A*.

The isopropylidene derivative was formed by boiling a solution of the hydrazide in acetone; white plates from acetone-heptane, m.p. 191–193°.

Anal. Calc'd for $C_{16}H_{21}N_3O_2S$: C, 60.2; H, 6.6; N, 13.2.
Found: C, 60.8; H, 6.6; N, 13.4.

trans-4-(N-Methylcarbanilido)thiophane-3-carboxylic acid. (*A*). A solution of 160 mg.

of *trans*-4-(N-methylcarbanilido)thiophane-3-carboxhydrazide (VIII) in 2 cc. of 6 *N* hydrochloric acid was heated on the steam-bath under reflux for fourteen hours. After a few minutes heating, white crystals separated, most of which did not redissolve. The crystals had m.p. 189–190°; yield, 75 mg. (50%). Recrystallization from dilute alcohol raised the m.p. to 190–191°.

Anal. Calc'd for $C_{13}H_{15}NO_3S$: C, 58.8; H, 5.7; N, 5.3.
Found: C, 59.1; H, 5.8; N, 5.0.

From the aqueous filtrate was isolated 7 mg. (7%) of thiophane-3,4-*trans*-dicarboxylic acid (II), m.p. 126–127°, resolidified and remelted at 136–137°, which gave no depression in m.p. when mixed with an authentic sample. A mixture with the thiophane-3,4-*cis*-dicarboxylic acid melted at 95–100°.

(*B*). A mixture of 670 mg. of thiophane-3,4-*trans*-dicarboxylic acid (II), 1 cc. of thionyl chloride, and 5 cc. of benzene was refluxed for thirty minutes, then evaporated *in vacuo*. To the residue in 10 cc. of benzene was added 0.4 cc. of methylaniline in 5 cc. of benzene dropwise with swirling over a period of about three minutes. After ten minutes, the mixture was extracted three times with aqueous sodium bicarbonate, acidified, saturated with salt, and cooled at 3°. The product was washed with cold water; yield, 90 mg. (9%), m.p. 178–180°. Several recrystallizations from dilute alcohol gave white crystals, m.p. 190–191°, identical with preparation *A*.

trans-3-Uranilino-4-(N-methylcarbanilido)thiophane. To a solution of 3.5 g. of *trans*-4-(N-methylcarbanilido)thiophane-3-carboxhydrazide (VIII) in 20 cc. of 1 *N* hydrochloric acid and 5 cc. of chloroform was added dropwise, with stirring and ice cooling, a solution of 0.94 g. of sodium nitrite in 20 cc. of water over a period of five minutes. After being stirred an additional one hour at 0°, the layers were separated and the aqueous phase extracted again with chloroform. The combined organic solutions were dried with sodium sulfate, refluxed for thirty minutes, and treated with 20 cc. of aniline. Evaporation of the solvent and trituration with methanol gave 3.3 g. (77%) of white crystals, m.p. 215–217°. Recrystallization from acetone raised the m.p. to 216–217°.

Anal. Calc'd for $C_{19}H_{21}N_3O_2S$: N, 11.8. Found: N, 12.2.

This compound failed to react with hot hydrazine due to its insolubility in the reagent.

trans-3-Carbethoxyamino-4-(N-methylcarbanilido)thiophane (IX). A solution of 7.9 g. of VIII in 1 *N* hydrochloric acid was treated with sodium nitrite as in the previous experiment. The dried chloroform extract was diluted with 100 cc. of absolute alcohol, refluxed for seventy-five minutes and evaporated. The residue was crystallized from dilute alcohol, white needles, m.p. 162–164°; yield 7.35 g. (84%).

Anal. Calc'd for $C_{15}H_{20}N_2O_3S$: C, 58.4; H, 6.5; N, 9.1.
Found: C, 59.0; H, 6.4; N, 9.5.

trans-3-Aminothiophane-4-carboxylic acid (X). A mixture of 4.9 g. of IX and 50 cc. of 48% hydrobromic acid was refluxed for three hours, then evaporated to dryness *in vacuo*. The residue was dissolved in 50 cc. of methanol and neutralized with concentrated ammonium hydroxide. After standing overnight at 3°, the mixture was filtered and the crystals washed with methanol; yield, 0.98 g. (42%), m.p. 223° dec. Crystallization of a similar preparation from water gave white crystals, m.p. 242–243° dec.

Anal. Calc'd for $C_5H_9NO_2S$: N, 9.5. Found: N, 9.6.

The N-benzoyl derivative was prepared in the usual manner with benzoyl chloride and dilute alkali at 5°; white crystals from water, m.p. 202–203°.

Anal. Calc'd for $C_{12}H_{13}NO_3S$: C, 57.3; H, 5.2; N, 5.6.
Found: C, 57.6; H, 5.1; N, 5.9.

trans-4-Uranilinothiophane-3-carboxylic acid (XI). A solution of 0.98 g. of *trans*-3-aminothiophane-4-carboxylic acid (X) in 13 cc. of 0.5 *N* sodium hydroxide was stirred at 0° with 1.1 cc. of phenyl isocyanate for one hour, then warmed on the steam-bath to destroy the excess isocyanate. The filtered solution was acidified and the oil which separated soon solidified to white crystals, m.p. 176° dec; yield, 1.52 g. (86%). Recrystallization from dilute methanol did not change the m.p.

Anal. Calc'd for $C_{12}H_{14}N_2O_3S$: C, 54.2; H, 5.3; N, 10.5.
Found: C, 53.8; H, 5.4; N, 10.8.

cis-4-Benzoylaminothiophane-3-carboxylic acid. A mixture of 1 g. of thiophane-3,4-*cis*-dicarboxylic acid monomethyl ester (V), 1.2 cc. of thionyl chloride, and 10 cc. of benzene was refluxed for twnety minutes, then evaporated to dryness *in vacuo.* The evaporation was repeated with 10 cc. of benzene. The residue was dissolved in 10 cc. of acetone and added dropwise to a stirred solution of 0.5 g. of sodium azide in 10 cc. of water at 20°. After being stirred an additional hour, the mixture was diluted with water and the oily azide extracted with two 25-cc. portions of cold chloroform. The extracts were dried with calcium chloride, 15 cc. of methanol was added and the solution was slowly evaporated. The residue of crude *cis*-4-carbomethoxyamino-3-carbomethoxythiophane did not crystallize.

Anal. Calc'd for $C_8H_{13}NO_4S$: N, 6.4. Found · N, 7.2.

The oil was refluxed for one hour with 10 cc. of 48% hydrobromic acid, diluted with water and evaporated to dryness *in vacuo.* The evaporation was repeated with 10 cc. of water. The residue was extracted five times with ethyl acetate and the extracts rejected. A solution of the residue in 10 cc. of water was made just alkaline with sodium hydroxide, then benzoylated in the usual manner with benzoyl chloride; white crystals from water, m.p. 188–189°.

Anal. Calc'd for $C_{12}H_{13}NO_3S$: C, 57.3; H, 5.2; N, 5.6.
Found: C, 57.3; H, 5.3; N, 5.5.

A mixture with the corresponding *trans* isomer, m.p. 202–203°, melted at 167–180°.

cis-4-Uranilino-3-carbomethoxythiophane (XIII). A chloroform solution of 3-carbomethoxythiophane-4-carboxazide from 1 g. of V was prepared as described in the previous experiment except that the acid chloride reaction with the sodium azide was carried out at 0°. This chloroform solution was refluxed for ninety minutes, when gas evolution was complete. After the addition of 2 cc. of aniline, the solution was refluxed for five minutes, then evaporated to dryness *in vacuo.* The residue, dissolved in ethyl acetate was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate, and dilute hydrochloric acid. Evaporation gave an oil which crystallized from a mixture of ether and petroleum ether. Recrystallization from the same solvents gave 0.45 g. (31%) of product, m.p. 115–120°. Further recrystallization did not change the m.p.

Anal. Calc'd for $C_{13}H_{16}N_2O_3S$: N, 10.0. Found: N, 10.3.

This ester was difficult to recrystallize as it tended to form an oil.

cis-4-Uranilinothiophane-3-carboxhydrazide (XIV). A mixture of 0.27 g. of *cis*-4-uranilino-3-carbomethoxythiophane (XIII) and 0.3 cc. of 100% hydrazine hydrate was heated on the steam-bath for one hour, then diluted with water; yield, 0.20 g. (74%), m.p. 176–184°. Recrystallization from water raised the m.p. to 183–185°.

Anal. Calc'd for $C_{12}H_{16}N_4O_2S$: C, 51.3; H, 5.8; N, 20.0.
Found: C, 51.0; H, 6.2; N, 20.6.

For preparative purposes it was much better not to purify XIII, as it involved considerable loss. When the crude ester was treated with hydrazine, then diluted with water and benzene, a 57% over-all yield of hydrazide, m.p. 174–176°, was obtained from thiophane-3,4-*cis*-dicarboxylic acid monomethyl ester (V) in contrast to a 23% yield when the intermediate ester was purified.

trans-3,4-Dicarbomethoxythiophane (III). (*A*). A solution of 500 mg. of thiophane-3,4-*trans*-dicarboxylic acid (II) in 3 cc. of methanol was treated with an excess of ethereal diazomethane. Evaporation left a quantitative yield of crystals, m.p. 51–53°. Recrystallization from ether-petroleum ether gave white crystals, m.p. 51.5–53°.

Anal. Calc'd for $C_8H_{12}O_4S$: C, 47.1; H, 5.9.
Found: C, 47.6; H, 6.1.

The corresponding *cis* dimethyl ester was an oil, b.p. 154–156° (13 mm.).

Anal. Calc'd for $C_8H_{12}O_4S$: C, 47.1; H, 5.9.
Found: C, 47.0; H, 6.5.

(*B*). To a solution of 10 g. of II in 350 cc. of methanol was added 15 cc. of acetyl chloride.

After being refluxed for thirty minutes, the solution was evaporated to dryness *in vacuo*; yield, 11.2 g. (96%) of product, m.p. 49–51°.

Thiophane-3,4-trans-dicarboxylic acid monomethyl ester (*XVII*). A solution of 11.2 g. of *trans*-3,4-dicarbomethoxythiophane (III) in 50 cc. of methanol and 20 cc. of 10% sodium hydroxide was refluxed for twenty minutes, then concentrated to about one-third the volume. The solution was diluted with water containing excess sodium bicarbonate and washed with benzene. Evaporation of the benzene gave 3 g. of unchanged diester.

The aqueous layer was acidified, extracted twice with chloroform, and evaporated to dryness; yield, 8 g. of an oil which did not crystallize. It was characterized by conversion in 56% yield to the methylanilide (VII) through the acid chloride as described for the corresponding *cis* methylanilide, VI, m.p. and mixed m.p. 119–123°.

trans-4-Uranilino-3-carbomethoxythiophane (*XVI*). From 3.8 g. of thiophane-3,4-*trans*-dicarboxylic acid monomethyl ester (XVII) was obtained 3.9 g. (70%) of product, m.p. 130–134°, in the same manner as for the corresponding *cis* compound. Recrystallization from methanol gave white crystals, m.p. 134–135°.

Anal. Calc'd for $C_{13}H_{16}N_2O_3S$: C, 55.7; H, 5.8.
Found: C, 55.9; H, 5.7.

trans-4-Uranilinothiophane-3-carboxhydrazide (*XX*). A mixture of 3 g. of XVI, 6 cc. of 100% hydrazine hydrate, and 75 cc. of methanol was refluxed with stirring on the steam-bath for seventy minutes. The cooled mixture was filtered; yield, 2.55 g. (85%) of white crystals, m.p. 210–212° which was unchanged on recrystallization from water.

Anal. Calc'd for $C_{12}H_{16}N_4O_2S$: C, 51.3; H, 5.8; N, 20.0.
Found: C, 51.7; H, 5.5; N, 20.7.

4-Carbanilido-5-ketoimidazolido[4,5,c,cis]thiophane (*XXII*). To a stirred solution of 1.9 g. of *cis-4*-uranilinothiophane-3-carboxhydrazide (XIV) in 70 cc. of 1 *N* hydrochloric acid and 50 cc. of chloroform was added dropwise a solution of 0.56 g. of sodium nitrite with ice cooling over a period of ten minutes. The temperature was 5–7°. After being stirred for ten minutes more, the chloroform layer was separated and the aqueous phase extracted once more with chloroform. The combined extracts, dried with sodium sulfate at 0°, were refluxed for four hours. The chloroform was evaporated *in vacuo* and the residue extracted with hot benzene. Addition of heptane gave 1.17 g. (66%) of product, m.p. 156–158°. Recrystallization from benzene-petroleum ether gave white crystals, m.p. 164–167°.

Anal. Calc'd for $C_{12}H_{13}N_3O_2S$: C, 54.7; H, 5.0; N, 16.0.
Found: C, 54.5; H, 5.6; N, 15.7.

When ethyl acetate was used as a solvent instead of chloroform and the solution refluxed for seventy-five minutes, a cleaner product was obtained in 66% yield, m.p. 158–161°.

trans-3,4-Diuranilinothiophane (*XIX*). (*A*). From the diacid chloride of 1 g. of thiophane-3,4-dicarboxylic acid was obtained 1.1 g. (55%) of product, m.p. 225–229° dec. in the same manner as described for *cis*-3-carbomethoxy-4-uranilinothiophane (XIII). Recrystallization from dilute alcohol with the aid of Norit gave white crystals, m.p. 247° dec.

Anal. Calc'd for $C_{18}H_{20}N_4O_2S$: C, 60.7; H, 5.6.
Found: C, 60.8; H, 5.8.

(*B*) A solution of 0.5 g. *trans*-4-uranilinothiophane-3-carboxhydrazide (XX) in 1 *N* hydrochloric acid was treated in the same manner as described for the corresponding *cis* compound. Evaporation of the chloroform solution gave an oil with a strong isocyanate odor. It was dissolved in benzene and treated with 0.5 cc. of aniline. A solid immediately separated, yield, 0.33 g. (52%), m.p. 223° dec., identical with preparation *A*.

trans-3-Carbethoxyamino-4-uranilinothiophane (*XVIII*). (*A*). From 0.5 g. of *trans*-4-uranilinothiophane-3-carboxhydrazide (XX) was obtained 0.29 g. (52%) of product, m.p. 225–226° in the same manner as described for *trans*-3-carbethoxy amino-4-(N-methylcarbanilido)thiophane (IX). Recrystallization from dilute alcohol gave white crystals, m.p. 228–229°.

Anal. Calc'd for $C_{14}H_{19}N_3O_3S$: C, 54.3; H, 6.2; N, 13.6.
Found: C, 53.9; H, 6.0; N, 13.7.

(*B*). To a suspension of 200 mg. of *trans*-4-uranilinothiophane-3-carboxylic acid (XI) in 2 cc. of a solution of one drop of pyridine in 5 cc. of dry ether was added 1 cc. of thionyl chloride. After fifteen minutes with occasional shaking, the solution was evaporated to dryness *in vacuo* (bath 40°). The residual acid chloride was degraded to the urethan in the same manner as described for *cis*-3-carbomethoxy-4-carbomethoxy aminothiophane except that the sodium azide reaction was carried out at 0° and ethanol was substituted for methanol; yield, 130 mg. (54 %), m.p. 208–212°. A mixture with preparation *A* melted at 216–220°.

3,4-cis-Diaminothiophane (*XXI*) *dihydrobromide and dipicrate.* A mixture of 1.0 g. of 4-carbanilido-5-keto[4,5,c,*cis*]thiophane (XXII) and 10 cc. of 48% hydrobromic acid was refluxed for fifteen hours, then cooled in ice. The dihydrobromide was collected on a glass filter and washed with 48% hydrobromic acid, alcohol, and ether; yield, 260 mg. (25%), m.p. 307–309° dec. Recrystallization from 48% hydrobromic acid gave the pure salt, m.p. 309–310° dec.

Anal. Calc'd for $C_4H_{12}Br_2N_2S$: C, 17.1; H, 4.4; N, 10.0.
Found: C, 17.1; H, 4.4; N, 10.5.

The reaction mixture filtrate was combined with the washings and evaporated to dryness *in vacuo*. The residue was dissolved in water, 500 mg. of anhydrous sodium acetate and 500 mg. of picric acid were added, and the mixture was heated on the steam-bath for a few minutes. The dipicrate was collected and extracted with hot alcohol to remove excess picric acid; yield, 300 mg. (14%), m.p. 240° dec.

The dipicrate was also prepared from the dihydrobromide with aqueous sodium acetate and picric acid in quantitative yield.

Anal. Calc'd for $C_{16}H_{16}N_8O_{14}S$: C, 33.4; H, 2.8; N, 19.4.
Found: C, 33.7; H, 3.0; N, 19.1.

The *trans*-dipicrate was prepared in the same manner in 97% yield, m.p. 250° dec., from *trans*-3,4-diaminothiophane dihydrobromide (2). The m.p. of this compound has been recorded in the literature as 250° dec. (3).

cis-3,4-Dibenzoylaminothiophane. A solution of the solid *cis*-3,4-diaminothiophane (XXI) dihydrochloride from 200 mg. of the corresponding dipicrate in 5 cc. of 10% sodium hydroxide was shaken with 0.4 cc. of benzoyl chloride until a solid was formed. It was removed by filtration and washed with dilute sodium hydroxide, water, alcohol, and ether; yield, 50 mg. (47%), m.p. 227–229°. Recrystallization from alcohol gave white crystals, m.p 230–231°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2S$: C, 66.2; H, 5.6; N, 8.6.
Found: C, 66.5; H, 5.6; N, 8.9.

This compound was identical[1] with the dibenzoyl derivative of "isomer B" of 3,4-diaminothiophane described by Kilmer and McKennis (4) as melting at 238–239°.

5-Ketoimidazolido[4,5,c,cis]thiophane (*XXIII*). A solution of 260 mg. of *cis*-3,4-diaminothiophane (XXI) dihydrobromide in 50 cc. of saturated sodium bicarbonate was treated with phosgene at 0° until acidic to Congo Red paper. The solution was concentrated *in vacuo* to remove excess phosgene, then just neutralized with aqueous sodium bicarbonate. A test portion gave no precipitate when heated with picric acid. The solution was evaporated to dryness *in vacuo* and the residue extracted with hot butanol. Evaporation *in vacuo* left a solid residue which was partially inorganic. Sublimation at 155° (1 mm.) gave 60 mg. (45%) of white crystals, m.p. 231°.

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[1] We wish to thank Dr. George Bosworth Brown of the Department of Biochemistry, Cornell University Medical College for the mixed m.p. determination. He reported, "Your sample melts at 233–236° when heated rapidly on the hot stage microscope. It sublimes and, when heated slowly (2°/min.), the sublimate melts at 238–239°. The sample of Kilmer and McKennis also melts at 238–239° (sublimate). The mixed m.p. is 234° when heated rapidly and is 238° on the sublimate when heated at 2°/min. The crystalline form of both sublimates (needles) is identical."

Anal. Calc'd for $C_5H_8N_2OS$: C, 41.7; H, 5.6.
Found: C, 41.7; H, 5.6.

The corresponding *trans*-diamine when treated under the same conditions failed to react, as the diamine dipicrate could be recovered quantitatively.

3-Phenyl-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil (XV). A solution of 1.0 g. of *cis* 4-uranilinothiophane-3-carboxhydrazide (XIV) in 20 cc. of 6 *N* hydrochloric acid was heated on the steam-bath for two hours. During this time crystals of the uracil began to separate. The cooled mixture was filtered and the product washed with water, methanol, and ether; yield, 0.65 g. (74%) of white crystals, m.p. 237–238°. Recrystallization from Methyl Cellosolve raised the m.p. to 238–239°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2S$: C, 58.1; H, 4.9; N, 11.3.
Found: C, 58.1; H, 5.4; N, 11.2.

When *trans*-4-uranilinothiophane-3-carboxhydrazide (XX) was treated under the same conditions a 63% yield of *trans*-4-uranilinothiophane-3-carboxylic acid (XI) was obtained.

Action of hydrazine on 3-phenyl-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil (XV). A solution of 100 mg. of the uracil in 0.1 cc. of 100% hydrazine hydrate was heated on the steam-bath for ten minutes during which time crystals separated from solution. Dilution with water gave 105 mg. (92%) of *cis*-4-uranilinothiophane-3-carboxhydrazide, XIV, m.p. and mixed m.p. 184–185°. The compound was readily soluble in 6 *N* hydrochloric acid and when the solution was heated on the steam-bath for one hour, the uracil, m.p. 238–239° was reformed in 81% yield.

When 100 mg. of the uracil was heated with 0.2 cc. of hydrazine for two hours, 40 mg. (35%) of a hydrazide was obtained, m.p. 191–193°. It was mainly the *trans* hydrazide, XX, as it gave *trans*-4-uranilinothiophane-3-carboxylic acid (XI), m.p. 169° dec., when heated with 6 *N* hydrochloric acid.

Action of sodium methoxide on 3-phenyl-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil (XV). To a boiling suspension of 100 mg. of the uracil in 3 cc. of methanol was added 20 mg. of sodium in 1 cc. of methanol. The uracil immediately dissolved. After being boiled for five minutes, the solution was acidified with acetic acid and most of the methanol was evaporated under an air stream on the steam-bath. The mixture, diluted with water, was extracted with benzene and the extract evaporated. Crystallization from ether gave 50 mg. (44%) of *trans*-3-carbomethoxy-4-uranilinothiophane (XVI), m.p. and mixed m.p. 132–133°. A mixture with the corresponding *cis* ester melted at 95–108°.

1-Acetyl-3-phenyl-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil (XII). (*A*). A mixture of 100 mg. of *trans*-4-uranilinothiophane-3-carboxylic acid (XI), 50 mg. of anhydrous sodium acetate, and 1 cc. of acetic anhydride was refluxed for ten minutes, then diluted to 10 cc. with water, and cooled. The white crystals were collected on a filter; yield, 75 mg. (69%), m.p. 238–240°. Recrystallization from Methyl Cellosolve gave white crystals, m.p. 240–241°. A mixture with XV melted at 208–212°.

Anal. Calc'd for $C_{14}H_{14}N_2O_3S$: C, 57.8; H, 4.9; N, 9.7.
Found: C, 57.6; H, 4.9; N, 9.7.

(*B*). A mixture of 100 mg. of XV, 50 mg. of anhydrous sodium acetate, and 2 cc. of acetic anhydride was refluxed for twenty minutes, then diluted to 20 cc. with water; yield, 110 mg. (quant.) of white crystals, m.p. 240–241°. A mixed m.p. with preparation *A* was the same.

The acetyl uracil (XII) was converted to *cis*-4-uranilinothiophane-3-carboxhydrazide (XIV) with hydrazine in 82% yield and to *trans*-3-carbomethoxy-4-uranilinothiophane (XVI) with methanolic sodium methoxide in the same manner as the non-acetylated uracil, XV.

The acetyl group was readily removed by hydrolysis. To a hot solution of 105 mg. of XII in 5 cc. of acetic acid was added 2 cc. of 6 *N* hydrochloric acid. After being heated on the steam-bath for thirty minutes, the solution was diluted to 25 cc. with water and cooled; yield, 70 mg. (78%) of XV, m.p. and mixed m.p. 237–239°.

SUMMARY

Methods for the synthesis of *cis*-3,4-diaminothiophane by the stepwise degradation of the carboxyl groups of either the *cis* or the *trans* form of thiophane-3,4-dicarboxylic acid have been described.

Pearl River, N. Y.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES]

BIOTIN. VI. SYNTHESIS OF BIOTIN AND *epi*ALLOBIOTIN

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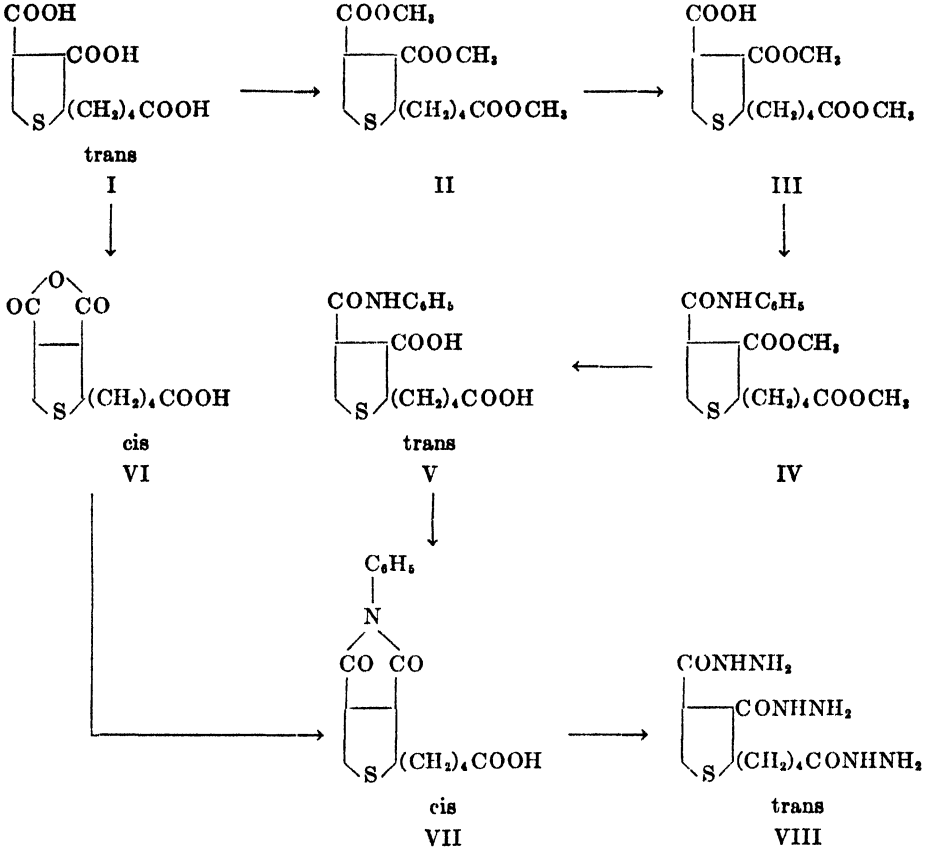
Methods of synthesizing 2-(δ-carboxybutyl)thiophane-3,4-*trans*-dicarboxylic acid (I), an intermediate in the projected synthesis of biotin, have been the subject of some previous communications (1, 2). The conversion of this triacid to 2-(δ-carboxybutyl)-3,4-diaminothiophane involves the selective degradation of the two ring carboxyls, leaving the side chain carboxyl intact. This has been accomplished by degrading the carboxyl groups one at a time and proving the structure of the intermediates at each step in order to demonstrate that the proper carboxyl group had been converted to an amine.

Treatment of the trimethyl ester (II) of I with one equivalent of alkali resulted in an oily diester monoacid, III, which gave a crystalline anilide, IV. If the side chain carboxyl group were the one that saponified, it would only be necessary to make a dihydrazide from the remaining two ester groups, then degrade them by the Curtius method. If one of the ring carboxyls saponified, then it would be necessary to degrade it *via* the acid chloride with sodium azide. That a free ring carboxyl group was present was proved in the following manner:

The diester, IV, was saponified to a carbanilido diacid, V. When this acid was boiled with propionic anhydride, inversion of configuration to *cis* and ring closure to 2-(δ-carboxybutyl)thiophane-3,4-*cis*-dicarboxanil (VII) took place. The structure was shown to be *cis* by treating 2-(δ-carboxybutyl)thiophane-3,4-*cis*-dicarboxylic anhydride (VI), prepared by inversion of the corresponding *trans* acid, with aniline followed by ring closure with acetyl chloride to the identical anil, VII.

As the two ring carboxyl groups in the anil, VII have been distinguished from the side chain free carboxyl group, it was considered possible that treatment with hydrazine would give 2-(δ-carboxybutyl)thiophane-3,4-*trans*-dicarboxhydrazide (3). However, under the conditions necessary to cleave the nitrogen ring, the side chain carboxyl group also surprisingly formed a hydrazide and the resultant product was the *trans*-trihydrazide (VIII). It was identified by comparison with the *trans*-trihydrazide prepared from the trimethyl ester (II).

As selective saponification of the triester took place on the ring, the free carboxyl in III was degraded by treating its acid chloride with sodium azide. The intermediate azide was rearranged to the isocyanate and condensed with aniline forming 2-(δ-carbomethoxybutyl)-3-carbomethoxy-*trans*-4-uranilinothiophane (IX). The crystalline ester was saponified to the corresponding *trans*-diacid, X. The position of the uranilino group was proved by hydrogenolysis of the 2-(δ-carboxybutyl)-4-uranilinothiophane-3-*trans*-carboxylic acid in 20% sodium hydroxide at 200–210° and 70 atmospheres of hydrogen in the presence of U.O.P. nickel catalyst. The product was α-ethylsuberic acid (XI), probably formed by hydrogenolysis of the sulfur, hydrolysis of the uranilino group, deamination of the resultant amino acid and reduction of the double bond. It

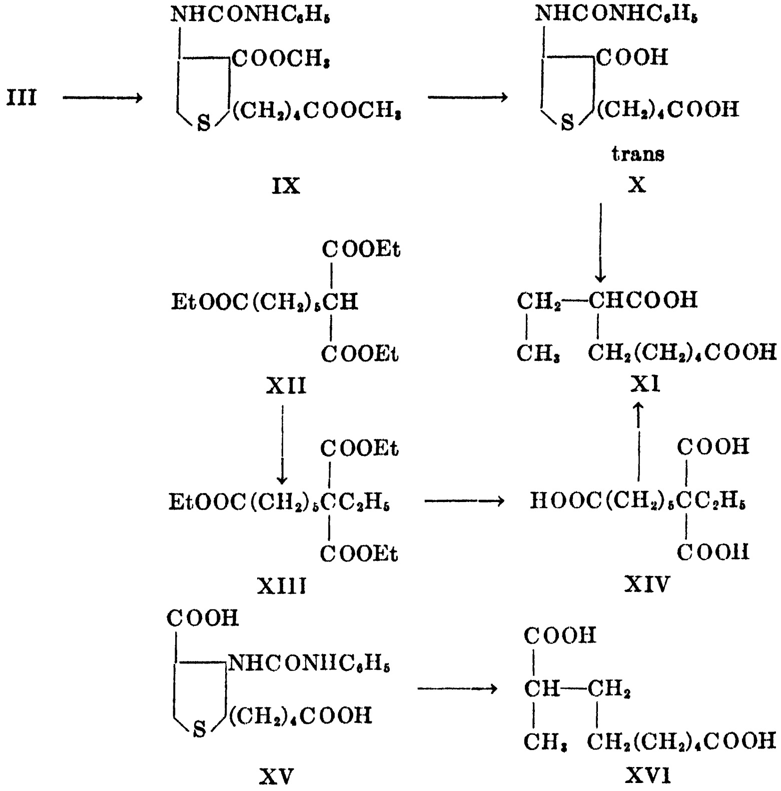


was identical with an authentic sample prepared from ethyl α-carbethoxysuberate as shown.

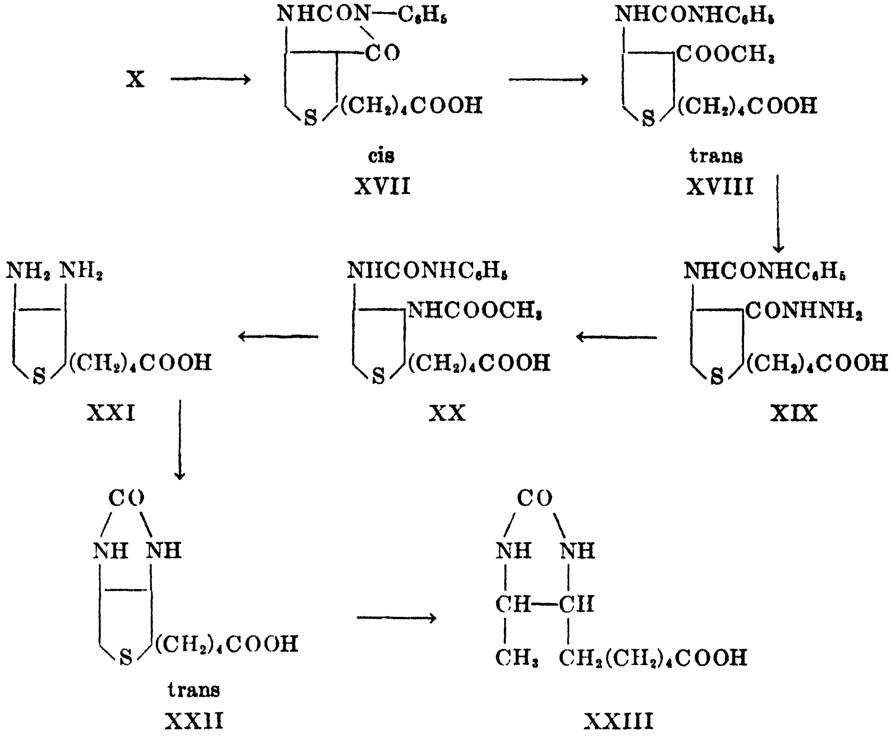
If the product of the Curtius degradation were the isomeric uranilino diacid, XV, then the hydrogenation product should have been α-methylazelaic acid (XVI).

A study of the selective hydrolysis of 2-(δ-carbomethoxybutyl)-3-carbomethoxy-*trans*-4-uranilinothiophane (IX) was made and although over twenty experiments were run, no clear-cut products could be obtained.

It was found possible to distinguish between the remaining two carboxyls by formation of 3-phenyl-6-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,*cis*] uracil (XVII) by methods worked out on the model uracil without a side chain described in the previous communication (4). By refluxing a solution of 2-(δ-carboxybutyl)-4-uranilinothiophane-*trans*-3-carboxylic acid (X) with acetic anhydride and sodium acetate, followed by hydrolysis of the 1-acetyl group with dilute hydrochloric acid, the *cis*-uracil, XVII, was obtained. The intermediate acetyl derivative could be isolated, but the over-all yield (63–76%) was much better if it was hydrolyzed without isolation. The nitrogen ring of the uracil (XVII) on short boiling with methanolic sodium methoxide was ruptured with inversion of configuration to form 2-(δ-carboxybutyl)-3-carbomethoxy-*trans*-4-uranilinothiophane (XVIII) in 74% yield. The monoester was easily converted to the *trans* hydrazide, XIX. The configuration was established as *trans* in two ways. Hydrolysis of the hydrazide with 6 *N* hydrochloric acid gave the *trans*-uranilino diacid, X. If the configuration had been *cis*, the uracil, XVII, would have been reformed. The second method was by Curtius degradation of the hydrazide, which formed a *trans* urethan, XX, rather than 2-(δ-carboxybutyl)-5-keto-6-carbanilidoimidazolido[4,5,c,*cis*]thiophane (XXVIII) (4). The 2-(δ-carboxybutyl)-3-carbomethoxyamino-*trans*-4-uranilinothiophane (XX) was hydrolyzed to the diamine, XXI, with aqueous barium hydroxide at 150°, which was isolated as the sulfate, m.p. 272–275° dec. Treatment with phosgene in aqueous potassium carbonate caused the separation of a *trans*-biotin isomer, XXII, with no definite melting point, but gradually decomposing over 185°.



Harris *et al.* (5) have described *dl*-biotin and two of its isomers. They reported *dl*-biotin to melt at 232°, *dl*-allobiotin to melt at 194–196° and *dl-epi*allobiotin to decompose without melting starting at 195°. Thus the biotin isomer, XXII, from its melting point, may be either *dl-epi*allobiotin or the unknown *dl-epi*biotin. This point was proved by desulfurization of XXII to the biologically inactive *dl*-desthioallobiotin (XXIII) (5). If XXII were *dl-epi*biotin, then the biologically active *dl*-desthiobiotin (5) would be formed on desulfurization. Thus the *trans*-biotin isomer, XXII, is *dl-epi*allobiotin. Therefore biotin and *epi*-biotin must be *cis* isomers and allobiotin a *trans* isomer.[1]



When the uracil valeric acid (XVII) was treated with hydrazine, ring cleavage occurred with partial inversion to a mixture of *cis* and *trans* hydrazides (XIX). This difficulty was attributed to the ready solubility of a hydrazide with a free carboxyl group in hydrazine. When the carboxyl group of the uracil was blocked by conversion to its anilide, XXIV, then hydrazine smoothly opened the uracil ring in 95% yield to the insoluble *cis*-hydrazide, XXVII. The configuration was established as *cis* in two ways. When the uracil anilide, XXIV, was treated with methanolic sodium methoxide, the *trans* methyl ester, XXV, was formed which was readily converted to the *trans*-hydrazide, XXVI. A mixture of the *cis* and *trans* hydrazides gave a depression in melting point.

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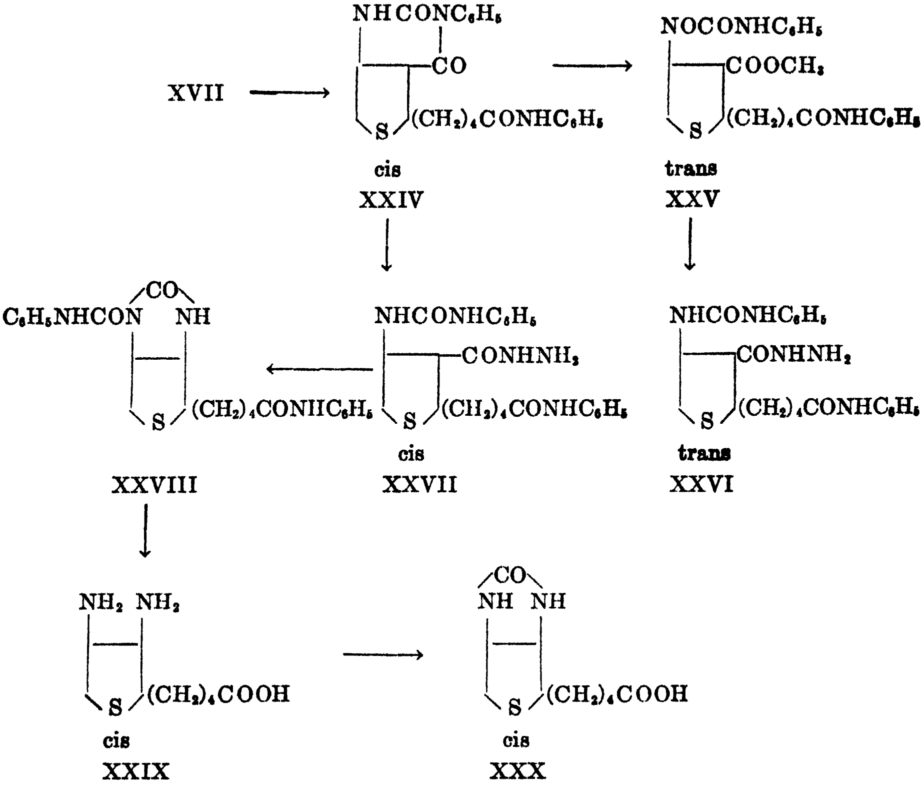
[1] Following the completion of this work, Harris and his co-workers (10) presented evidence that biotin was a derivative of a *cis*-diamine and that allobiotin and *epi*allobiotin were derived from *trans*-diamines. They also recorded (11) the m.p. of *dl-epi*allodiamine sulfate as 283–285° and *dl*-allodiamine sulfate as 228–230°. The m.p. of the former agrees with the m.p. of the sulfate of XXI.

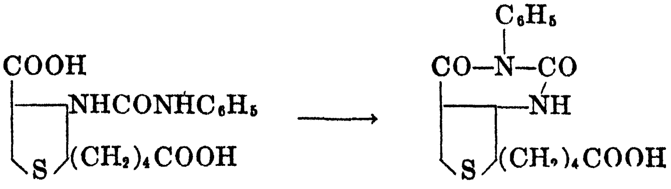
The second proof of configuration was conversion of the *cis*-hydrazide to 2-(δ-carbanilidobutyl) - 5 - keto - 6 - carbanilidoimidazolido[4,5,c,*cis*]thiophane (XXVIII) on diazotization. This ring formation of the isocyanate is characteristic of the *cis* series (4). The diazotization of the *cis*-hydrazide, XXVII, in the usual manner with sodium nitrite in 50% methanol which was 0.5 *N* in hydrochloric acid gave only traces of an azide, most of the hydrazide being recovered unchanged. However, when the diazotization was run at 100° with butyl nitrite in dry butanol containing hydrogen chloride (6), a 55% yield of the imidazolone, XXVIII, was obtained. Hydrolysis to the *cis*-diamine sulfate, XXIX, was accomplished smoothly by long heating with barium hydroxide solution at 160°. Treatment of the diamine with phosgene gave *dl*-biotin, m.p. 230–232°, which was 50% as active as natural biotin when assayed against *L. arabinosis* or yeast.



It should be pointed out that this method of synthesis offers chemical control of isomers and no fractional crystallizations are necessary in order to separate the isomers. The average yield of *dl*-biotin from pimelic acid is of the order of 1.7% or 2.7 g. per 100 g. of pimelic acid.

If the carboxyl group in the 3 position of the crystalline *trans* isomer of 2-(δ-carboxybutyl)thiophane-3,4-dicarboxylic acid (I) could be degraded to the

3-uranilino acid, XXXI, and converted to a *cis* uracil, XXXII, then inversion would take place at C_4 and the configuration of *epi*biotin would be obtained.



trans XXXI

cis XXXII

Work towards the preparation of XXXII, and *epi*biotin has been completed and will be described in a future communication.

Acknowledgment. The authors wish to thank Mr. Philip Weiss and Miss Barbara Eames for the microanalyses and Mr. A. Dornbush for the microbiological assays.

EXPERIMENTAL

2-(δ-Carbomethoxybutyl)-3,4-trans-dicarbomethoxythiophane (II). A mixture of 20.6 g. of 2-(δ-carboxybutyl)thiophane-3,4-*trans*-dicarboxylic acid (I), 125 cc. of methanol, 175 cc. of chloroform, and 5 cc. of concentrated sulfuric acid was refluxed for sixteen hours under a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The solution was washed with several volumes of water containing excess sodium bicarbonate. Distillation of the chloroform left 22.5 g. (94%) of the triester as an oil. In other runs the yield was 89–94%.

Anal. Calc'd for $C_{14}H_{22}O_6S$: C, 52.8; H, 7.0.
Found: C, 52.9; H, 7.0.

2-(δ-Carbomethoxybutyl)-3-carbomethoxythiophane-4-carboxylic acid (III). To a solution of 22.5 g. of the above trimethyl ester in 110 cc. of methanol was added 31 cc. of 10% sodium hydroxide. After a minimum of sixteen hours at room temperature, the solution was concentrated to about one-half its volume, diluted with 100 cc. of water and 300 cc. of saturated sodium bicarbonate solution, and extracted with benzene. The benzene extract on evaporation gave 6.4 g. (24%) of unchanged triester. The alkaline solution was acidified and extracted with benzene. The extract, washed with dilute hydrochloric acid, was evaporated leaving 17.6 g. (69%) of crude product.

In other runs the yield of recovered triester was 20–30% and the yield of product 60–70%. By saturation of the aqueous mother liquor with salt and extraction with ethyl acetate, the remainder of the triester could be accounted for as monoester diacids, which could be esterified and used again. As the latter are insoluble in benzene, satisfactory separation of the monoacid diesters from the monoester-diacids was readily accomplished.

2-(δ-Carbomethoxybutyl)-3-carbomethoxy-4-trans-carbanilidothiophane (IV). A solution of 5 g. of 2-(δ-carbomethoxybutyl)-3-carbomethoxythiophane-*trans*-4-carboxylic acid (III) and 5 cc. of thionyl chloride in 20 cc. of benzene was refluxed for fifteen minutes, when gas evolution was complete. The solvent was removed *in vacuo* (bath 45°) and the evaporation repeated with 25 cc. of benzene. The residue was dissolved in 50 cc. of benzene and treated with 6 cc. of aniline. After ten minutes the solution was washed twice with dilute hydrochloric acid, aqueous sodium bicarbonate and water. Solvent was evaporated and the residue crystallized from methanol; yield, 2.4 g. (38%), m.p. 116–119°. Repeated recrystallization from methanol failed to raise the m.p. above 118–124°.

Anal. Calc'd for $C_{19}H_{25}NO_5S$: C, 60.2; H, 6.6; N, 3.7.
Found: C, 60.2; H, 6.3; N, 4.2.

2-(δ-Carboxybutyl)-4-carbanilidothiophane-3-trans-carboxylic acid (V). To a solution of 3 g. of the above ester, IV, in 25 cc. of hot methanol was added 12 cc. of 10% sodium hydroxide. The solution was boiled down on the steam-bath for one hour, then diluted with 20 cc. of water, and acidified. The product was washed with water; yield 2.75 g. (98%), m.p. 238–242°. Recrystallization from alcohol gave white crystals, m.p. 253–255°.

Anal. Calc'd for $C_{17}H_{21}NO_5S$: C, 58.2; H, 6.0; N, 4.0.
Found: C, 58.2; H, 6.1; N, 3.6.

2-(δ-Carboxybutyl)thiophane-3,4-cis-dicarboxylic anhydride (VI). A mixture of 500 mg. of 2-(δ-carboxybutyl)thiophane-3,4-*trans*-dicarboxylic acid (I), 150 mg. of anhydrous sodium acetate and 5 cc. of acetic anhydride was refluxed for thirty minutes, then diluted with 5 cc. of water containing 0.3 cc. of concentrated hydrochloric acid. After the excess anhydride had decomposed, the solution was evaporated to dryness *in vacuo* and extracted with acetone. The acetone was concentrated to a small volume and diluted with benzene almost to turbidity. After standing overnight the crystals of *cis*-triacid were collected; yield, 240 mg. As the triacid appeared to be hygroscopic and difficult to handle it was converted to the anhydride by evaporative distillation at 190° (1 mm.). The crystalline distillate was purified by recrystallization from chloroform-petroleum ether, white crystals, m.p. 110–111°.

Anal. Calc'd for $C_{11}H_{14}O_5S$: C, 51.2; H, 5.5.
Found: C, 51.5; H, 6.2.

2-(δ-Carboxybutyl)thiophane-3,4-cis-dicarboxanil (VII). (*A*). A solution of 1.9 g. of 2-(δ-carboxybutyl)-4-carbanilidothiophane-3-*trans*-carboxylic acid (V) in 20 cc. of propionic anhydride was refluxed for two hours. After the cautious addition of 20 cc. of water, the solution was refluxed for fifteen minutes, then diluted to about 200 cc. with water. The product weighed 1.22 g (68%), m.p. 134–136°. Recrystallization from water containing a little acetic acid raised the m.p. to 136–139°.

Anal. Calc'd for $C_{17}H_{19}NO_4S$: C, 61.3; H, 5.8; N, 4.2.
Found: C, 61.2; H, 6.1; N, 4.8.

(*B*). To a solution of 100 mg. of 2-(δ-carboxybutyl)thiophane-3,4-*cis*-dicarboxylic anhydride (VI) in 5 cc. of hot chloroform was added 0.1 cc. of aniline. A gummy anilic acid immediately separated which could not be crystallized, indicating that ring opening had taken place in two ways. After the addition of 10 cc. of benzene, the solvent was decanted from the anilic acid. The latter was cyclized by refluxing its solution in 10 cc. of acetyl chloride for fifteen minutes. The acetyl chloride was evaporated and the oily residue was heated on the steam-bath with 4 cc. of 50% acetic acid for ten minutes, then diluted to 25 cc. with water; yield, 60 mg. (46%), m.p. and mixed m.p. with preparation *A*, 136–138°.

Trihydrazide of 2-(δ-carboxybutyl)thiophane-3,4-trans-dicarboxylic acid (VIII). A solution of 1.05 g. of 2-(δ-carboxybutyl)thiophane-3,4-*cis*-dicarboxanil (VII) in 2.5 cc. of 100% hydrazine hydrate was heated on the steam-bath under reflux for fourteen hours, then dissolved in 20 cc. of methanol. The product soon crystallized from the solution; yield, 0.36 g. (38%), m.p. 218–220°. The trihydrazide is readily soluble in water.

Anal. Calc'd for $C_{11}H_{22}N_6O_3S$: N, 26.4. Found: N, 26.4.

The methanol filtrate was evaporated to dryness and treated with 2 cc. of hydrazine again. An additional 0.23 g. (total, 62%) of product was obtained, m.p. 215-217°.

The tribenzylidine derivative formed rapidly in hot dilute alcohol in 98% yield. It was purified by recrystallization from Methyl Cellosolve, white crystals, m.p. 212–214°.

Anal. Calc'd for $C_{32}H_{34}N_6O_3S$: N, 14.5. Found: N, 14.5.

This compound was insoluble in hot aqueous sodium bicarbonate or 3% alkali.

The reaction was also run on the anil, VII, with hydrazine containing one equivalent of sodium hydroxide. The trihydrazide was again isolated. The filtrate was treated with benzaldehyde, but no water-insoluble, alkali-soluble dibenzylidine derivative was formed.

2-(δ-Carboxybutyl)-4-uranilinothiophane-trans-3-carboxylic acid (X) and dimethyl ester (IX). (*A*). A mixture of 11.8 g. of crude 2-(δ-carbomethoxybutyl)-3-carbomethoxythiophane-4-*trans*-carboxylic acid (III), 12 cc. of thionyl chloride and 50 cc. of benzene was refluxed for fifteen minutes, then evaporated to dryness *in vacuo* (bath 50°). After the addition of 25 cc. of benzene, the evaporation was repeated. The residual acid chloride, cooled in an ice-bath, was dissolved in 50 cc. of acetone and added dropwise with stirring and ice cooling to a solution of 3.1 g. of sodium azide in 50 cc. of water at such a rate that the temperature was just below 10°. After being stirred one hour at 0°, the mixture was diluted with several volumes of water and the oily azide extracted twice with chloroform. The combined extracts, after being dried with calcium chloride at 0°, were refluxed for thirty minutes, treated with 5 cc. of aniline and refluxed five minutes longer. Washed with dilute hydrochloric acid, the solution was evaporated to dryness and the residue crystallized from 60 cc. of methanol at 0°. The dimethyl ester (IX) was washed with ice cold methanol; yield, 6 g. (39%) of crystals, m.p. 124–128°.

Anal. Calc'd for $C_{19}H_{26}N_2O_5S$: N, 7.1. Found: N, 7.2.

The combined filtrate and washings were diluted with 25 cc. of 10% sodium hydroxide and boiled on the steam-bath for one hour, then diluted with water and clarified with Norit. Acidification gave a gummy precipitate which was suspended in ethyl acetate and shaken or stirred until the lumps had disintegrated. After standing overnight to complete crystallization, the diacid was washed with ethyl acetate; yield, 2.7 g. (19%) of product, m.p. 188° dec.

In other runs the diester was not isolated, but the mixture hydrolyzed directly. The yield of diacid was 40–45%.

(*B*) To a hot solution of 2.6 g. of 2-(δ-carbomethoxybutyl)-3-carbomethoxy-*trans*-4-uranilinothiophane (IX) in 50 cc. of methanol was added 15 cc. of 10% sodium hydroxide solution. After being boiled on the steam-bath for one hour, during which time most of the methanol evaporated, the solution was diluted with water, clarified with Norit, and acidified. The diacid, X, weighed 2.2 g. (92%), m.p. 182–183° dec. It was purified by recrystallization from dilute alcohol, white crystals, m.p. 190–191° dec.

Anal. Calc'd for $C_{17}H_{22}N_2O_5S$: C, 55.7; H, 6.1; N, 7.7.
Found: C, 55.9; H, 6.2; N, 8.0.

α-Ethyl-α-carboxysuberic acid (XIV). Ethyl α-carbethoxysuberate (XII) was prepared in 87% yield essentially according to procedure of Wood and duVigneaud (7) except that 1:2 absolute alcohol-benzene was used as a solvent and a little sodium iodide was added as a catalyst.

To a solution of 1.6 g. of sodium methoxide (Mathieson Alkali Works) in 10 cc. of absolute alcohol was added 8 g. of ethyl α-carbethoxysuberate and 4 cc. of ethyl iodide. After being refluxed for fifteen hours, the solution was acidified with acetic acid and most of the alcohol evaporated. The residue was diluted with water containing some sodium bisulfite and extracted with benzene. The benzene extract was washed with water and evaporated. Saponification of the ester with 9 g. of potassium hydroxide in 18 cc. of water diluted with 20 cc. of alcohol was complete after the mixture was heated on the steam-bath for three hours. The cooled solution, diluted with 25 cc. of water was acidified. After standing overnight the product was washed with water; yield, 4.6 g. (65%), m.p. 155–156° dec. A sample was recrystallized from ethyl acetate, white crystals, m.p. 155–156° dec.

Anal. Calc'd for $C_{11}H_{18}O_6$: C, 53.7; H, 7.4.
Found: C, 54.1; H, 7.7.

α-Ethylsuberic acid (XI). A mixture of 4.1 g. of α-ethyl-α-carboxysuberic acid and a trace of copper oxide was heated at 175–180° for fifteen minutes when gas evolution was complete. The crystalline residue obtained on cooling was purified by recrystallization from benzene-heptane with the aid of Norit; yield, 2.9 g. (87%), m.p. 74–75°.

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.3; H, 9.0.
Found: C, 58.9; H, 9.3.

The *p*-phenylphenacyl ester, prepared according to Shriner and Fuson (8), formed white crystals from methanol-acetone, m.p. 80–81°.

Anal. Calc'd for $C_{38}H_{38}O_6$: C, 77.2; H, 6.5.
Found: C, 77.2; H, 6.1.

The S-benzyl isothiouronium salt was prepared in water and recrystallized from isopropyl alcohol; white crystals, m.p. 145–146°.

Anal. Calc'd for $C_{26}H_{38}N_4O_4S_2$: C, 58.3; H, 7.2; N, 10.5.
Found: C, 58.6; H, 7.7; N, 10.3.

Hydrogenolysis of 2-(δ-carboxybutyl)-4-uranilinothiophane-3-trans-carboxylic acid (*X*). A mixture of 450 mg. of the uranilino acid (X), 4.5 g. of pulverized U.O.P. nickel catalyst (Universal Oil Products Co.), and 10 cc. of 20% sodium hydroxide was shaken with hydrogen at 70 atm. and 200–210° for twenty-two hours. The bomb contents were rinsed out with 200 cc. of 1% sodium hydroxide and the mixture heated on the steam-bath with occasional mixing for twenty minutes. The catalyst was removed by filtration through Celite and washed with water. The filtrate was acidified and extracted with ethyl acetate. Removal of the solvent left an oil which rapidly evaporatively distilled at 150° (1 mm.) and partially solidified on the cold finger; yield, 100 mg.

The crude *p*-phenylphenacyl ester was an oil which crystallized on seeding with the *p*-phenylphenacyl ester of α-ethylsuberic acid. It was purified by recrystallization from methanol-acetone, white crystals, m.p. 79–81°. A mixture with the *p*-phenylphenacyl ester of α-ethylsuberic acid melted at 80–81°.

The S-benzyl isothiouronium salt was prepared in water and recrystallized from isopropyl alcohol; white crystals, m.p. 145–146°. A mixture with the S-benzyl isothiouronium salt of α-ethylsuberic acid gave no depression in m.p.

Anal. Calc'd for $C_{26}H_{38}N_4O_4S$: N, 10.5. Found: N, 10.4.

3-Phenyl-6-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil (*XVII*). A mixture of 6.3 g. of 2-(δ-carboxybutyl)-4-uranilinothiophane-*trans*-3-carboxylic acid (X), 6.3 g. of sodium acetate and 130 cc. of acetic anhydride was refluxed in an oil-bath for one hour, then diluted cautiously with 65 cc. of water. After the acetic anhydride had decomposed, the solution was diluted with 60 cc. of concentrated hydrochloric acid and refluxed thirty minutes. The hot solution was clarified with Norit, using 50% acetic acid as a wash, then evaporated to a paste *in vacuo*, diluted with water and the product collected on a filter; yield, 3.8 g. (63%), m.p. 191° dec.

In other runs the yields were 63–76% probably depending upon the purity of the starting material. For analysis a sample was recrystallized from dilute methanol, white crystals, m.p. 202–203°.

Anal. Calc'd for $C_{17}H_{20}N_2O_4S$: C, 58.7; H, 5.8; N, 8.0.
Found: C, 58.5; H, 6.3; N, 7.6.

The 1-acetyl derivative can be isolated in 42% yield, m.p. 186–194°, by eliminating the hydrochloric acid and second heating period. Recrystallization from dilute alcohol gave white crystals, m.p. 191–195°.

Anal. Calc'd for $C_{19}H_{22}N_2O_5S$: C, 58.4; H, 5.7.
Found: C, 58.5; H, 5.4.

2-(δ-Carboxybutyl)-3-carbomethoxy-trans-4-uranilinothiophane (*XVIII*). To a boiling mixture of 1.0 g. of XVII and 40 cc. of methanol was added a solution of 120 mg. of sodium in 8 cc. of methanol. After being boiled on the steam-bath for fifteen minutes, the solution was acidified with 0.8 cc. of acetic acid, diluted with water until turbid, and cooled in an ice-bath; yield, 0.80 g. (74%), m.p. 134–135°. Recrystallization from dilute methanol did not raise the m p.

Anal. Calc'd for $C_{18}H_{24}N_2O_5S$: C, 56.8; H, 6.4; N, 7.4.
Found: C, 56.5; H, 6.5; N, 7.7.

The ester was hydrolyzed in quantitative yield by heating one hour with 3 *N* hydrochloric acid in 50% acetic acid to 2-(δ-carboxybutyl)-4-uranilinothiophane-*trans*-3-carboxylic acid (X) and identified by mixed m.p.

2-(δ-Carboxybutyl)-4-uranilinothiophane-trans-3-carboxhydrazide (*XIX*). A solution of 500 mg. of 2-(δ-carboxybutyl)-3-carbomethoxy-*trans*-4-uranilinothiophane (XVIII) in 1 cc. of 100% hydrazine hydrate was heated on the steam-bath for fifteen minutes, diluted with water and acidified with acetic acid. The somewhat gelatinous product was collected on a filter, washed with water, and dried on the steam-bath; yield, 450 mg. (90%) of white solid, m.p. 223° dec.

Anal. Calc'd for $C_{17}H_{24}N_4O_4S$: C, 53.7; H, 6.4; N, 14.7.
Found: C, 53.6; H, 6.6; N, 14.2.

When 20 mg. of this hydrazide was heated with 1 cc. of 6 *N* hydrochloric acid and 1 cc. of acetic acid for one hour, 2-(δ-carboxybutyl)-4-uranilinothiophane-3-*trans*-carboxylic acid (X) crystallized on cooling, m.p. and mixed m.p. 181°. A mixture with 3-phenyl-6-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (XVII) gave a depression in m.p.

2-(δ-Carboxybutyl)-3-carbomethoxyamino-4-trans-uranilinothiophane (*XX*). A mixture of 660 mg. of the above hydrazide (XIX), 51 cc. of methanol and 51 cc. of 0.33 *N* hydrochloric acid was heated until solution took place, then cooled in an ice-bath. A solution of 150 mg. of sodium nitrite in 10 cc. of water was added dropwise with stirring over a period of ten minutes. After being stirred an additional ten minutes at 0°, the mixture was diluted with ice-water and the azide extracted with ethyl acetate. The extract, dried with magnesium sulfate at 0°, was diluted with one-half volume of methanol and refluxed for thirty minutes. Solvent was evaporated and the residue triturated with ethyl acetate; yield 430 mg. (63%), m.p. 203–204° dec. Recrystallization from methanol did not change the m.p.

Anal. Calc'd for $C_{18}H_{25}N_3O_5S$: C, 54.7; H, 6.4; N, 10.3.
Found: C, 54.9; H, 7.0; N, 10.3.

2-(δ-Carboxybutyl)-trans-3,4-diaminothiophane (*XXI*) *sulfate* (*dl-epiallodiamine sulfate*). A mixture of 430 mg. of 2-(δ-carboxybutyl)-3-carbomethoxyamino-*trans*-4-uranilinothiophane (XX), 4 g. of barium hydroxide, and 10 cc. of water was shaken in a bomb at 150° for twenty hours. The bomb contents were rinsed out with water and excess baryta removed with dry ice. The filtrate from the barium carbonate was washed three times with chloroform to remove aniline, then made just acidic to Congo Red with 1 *N* sulfuric acid. After removal of the barium sulfate the solution was evaporated to dryness *in vacuo* and the residue triturated with methanol; yield, 210 mg. (61%) of white crystals which decomposed between 250–260°. Recrystallization from water raised the m.p. to 272–275° dec.

Anal. Calc'd for $C_9H_{20}N_2O_6S_2$: C, 34.2; H, 6.4.
Found: C, 33.6; H, 6.7.

Harris, *et al.* (11) give the m.p. of *dl-epi*allodiamine sulfate as 283–285° and *dl*-allodiamine sulfate as 228–230°.

2-(δ-Carboxybutyl)-5-ketoimidazolido[4,5,c,trans]thiophane (*XXII*) (*dl-epiallobiotin*). A solution of 900 mg. of 2-(δ-carboxybutyl)-3,4-*trans*-diaminothiophane (XXI) sulfate in 120 cc. of 10% potassium carbonate solution was treated with phosgene at 0° until acidic. The product was washed with ice-water; yield, 450 mg. (65%) of white crystals which gradually decompose over 185°. On recrystallization from 50% methanol it formed long white needles which had the same m.p. However, when plunged into a block at 215°, it melted with decomposition in forty seconds.

Anal. Calc'd for $C_{10}H_{16}N_2O_3S$: C, 49.2; H, 6.6; N, 11.5.
Found: C, 48.9, 48.7; H, 7.3, 6.7; N, 11.5.

The methyl ester, prepared from the acid in methanol with ethereal diazomethane, formed white needles from dilute methanol, micro m.p. 150–151°.

Anal. Calc'd for $C_{11}H_{18}N_2O_3S$: C, 51.2; H, 7.0; N, 10.8.
Found: C, 51.4; H, 7.5; N, 11.0.

The sulfur was removed from the acid by hydrogenolysis with Raney nickel at room temperature in dilute aqueous sodium bicarbonate. The product, *dl*-desthioallobiotin (XXIII) was purified by recrystallization from water, m.p. 163–165°. This compound had no biotin activity when assayed by the yeast method.

Anal. Calc'd for $C_{10}H_{18}N_2O_3$: N, 13.1. Found: N, 12.8.

Harris, *et al.* (5) give the m.p. of *dl-epi*allobiotin as gradually decomposing over 195° and *dl*-desthioallobiotin as 165–166°. They reported that the latter was inactive for the growth of yeast.

3-Phenyl-6-(δ-carbanilidobutyl)-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil (*XXIV*). A mixture of 3 g. of 3-phenyl-6-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (XVII), 12 cc. of dry ether containing 0.5% pyridine and 24 cc. of thionyl chloride was shaken at room temperature until solution was complete (fifteen minutes). The solution was evaporated to dryness *in vacuo* (bath 40°). The residual, partially crystalline, acid chloride was suspended in 150 cc. of acetone at 0°, 7.8 cc. of aniline was added and the mixture shaken until most of the acid chloride had dissolved. The reaction was then finished by slight warming on the steam-bath. The solution was diluted with 60 cc. of water, 7.8 cc. of concentrated hydrochloric acid was added, then the solution was diluted to about 900 cc. with water. The solid had m.p. 200–203°; yield, 3.55 g. (95%). A sample was purified for analysis by recrystallization from dilute acetone, white crystals, m.p. 212–213°.

Anal. Calc'd for $C_{23}H_{25}N_3O_3S$: C, 65.2; H, 6.0; N, 9.9.
Found: C, 65.1; H, 6.0; N, 9.5.

2-(δ-Carbanilidobutyl)-4-uranilinothiophane-cis-3-carboxhydrazide (*XXVII*). A mixture of 0.50 g. of XXIV and 4 cc. of 100% hydrazine hydrate was heated on the steam-bath with mixing for twenty minutes. At no time was solution complete, but the mixture became more pasty as the reaction proceeded. After dilution with water, the white solid was collected and dried on the steam-bath, m.p. 210–212° dec.; yield, 510 mg. (95%).

Anal. Calc'd for $C_{23}H_{29}N_5O_3S$: C, 60.7; H, 6.4.
Found: C, 61.1; H, 6.2.

If the uracil valeric acid, XVII, was treated with hydrazine in the same manner, it appeared that the product was a mixture of *cis* and *trans* hydrazides, probably due to the solubility of the product in the reagent.

2-(δ-Carbanilidobutyl)-3-carbomethoxy-4-trans-uranilinothiophane (*XXV*). (*A*). To a boiling suspension of 100 mg. of XXIV in 5 cc. of methanol was added 20 mg. of sodium methoxide in 1 cc. of methanol. The mixture rapidly became homogeneous. After being boiled for five minutes, the solution was acidified with acetic acid and diluted to about 25 cc. with water; yield, 98 mg. (91%), m.p. 171–174°. Recrystallization from chloroform-methanol gave white crystals, m.p. 187–190°.

Anal. Calc'd for $C_{24}H_{29}N_3O_4S$: C, 63.3; H, 6.4.
Found: C, 63.1; H, 6.6.

(*B*). A mixture of 250 mg. of 2-(δ-carboxybutyl)-3-carbomethoxy-4-*trans*-uranilinothiophane (XVIII), 1 cc. of thionyl chloride, and 2 cc. of a solution of one drop of pyridine in 5 cc. of dry ether was shaken occasionally for fifteen minutes at room temperature. The solution was evaporated to dryness *in vacuo* (bath 40°), the residue dissolved in 3 cc. of acetone and treated with 0.6 cc. of aniline. After five minutes the solution was diluted with water containing 1 cc. of concentrated hydrochloric acid; yield, 280 mg. (93%), m.p. 170–175°. Recrystallization from methanol raised the m.p. to 186–188°. A mixture with preparation *A* gave no depression in m.p.

2-(δ-Carbanilidobutyl)-4-uranilinothiophane-3-trans-carboxhydrazide (*XXVI*). A mixture of 100 mg. of 2-(δ-carbanilidobutyl)-3-carbomethoxy-*trans*-4-uranilinothiophane (XXV) and 0.8 cc. of hydrazine hydrate was heated on the steam-bath with mixing for twenty minutes. At no time did solution take place, but the mixture became more pasty as the reaction proceeded. The mixture was diluted with water and the hydrazide removed; yield, 85 mg. (85%) of white crystals, m.p. 238–239° dec.

Anal. Calc'd for $C_{23}H_{29}N_5O_3S$: C, 60.7; H, 6.3.
Found: C, 61.0; H, 6.3.

A mixture with the corresponding *cis*-hydrazide (XVII, m.p. 210–212° dec.) melted at 196–197° dec.

2-(δ-Carbanilidobutyl)-5-keto-6-carbanilidoimidazolido[4,5,c,cis]thiophane (*XXVIII*). To a hot suspension of 3.7 g. of 2-(δ-carbanilidobutyl)-4-uranilinothiophane-3-*cis*-carboxhydrazide (XXVII) in 125 cc. of dry butanol was added a solution of 0.42 g. of hydrogen chloride in 5 cc. of butanol. To the clear solution was added 1.04 cc. of butyl nitrite with swirling. The solution was then heated on the steam-bath for one hour, gas evolution being complete in five minutes. Solvent was removed *in vacuo*, the residue cooled and triturated with methanol; yield, 1.83 g. (51%), m.p. 198–205°. From the filtrate an additional 0.26 g. (7%), m.p. about 180° was obtained.

A similar preparation was purified for analysis by recrystallization from methanol; white crystals, m.p. 214–216°.

Anal. Calc'd for $C_{23}H_{26}N_4O_3S$: C, 63.0; H, 6.0; N, 12.8.

Found: C, 63.0; H, 6.3; N, 12.6.

Attempts to carry out the Curtius degradation in the usual manner as described for the *trans* hydrazide, XIX, gave only traces of product which could not be isolated, but could be detected by hydrolysis of the mixture, treatment with phosgene, and bioassay of the resultant solution.

2-(δ-Carboxybutyl)-3,4-cis-diaminothiophane (XXIX) sulfate. A mixture of 17 g. of 2-(δ-carbanilidobutyl)-5-keto-6-carbanilidoimidazolido[4,5,c,cis]thiophane (XXVIII), 85 cc. of 50% methanol, and 68 g. of barium hydroxide octahydrate was heated and shaken in a bomb at 160° for forty-five hours. The bomb contents were rinsed out with water and the excess baryta removed with dry ice. The filtrate, washed three times with chloroform to remove aniline, was made just blue to Congo Red by the addition of 1 *N* sulfuric acid. After removal of the barium sulfate the solution was evaporated to dryness *in vacuo* and triturated with methanol. The almost colorless crystals were washed with methanol, m.p. 254–256° dec.; yield, 10.1 g. (83%).

For analysis a sample was recrystallized by solution in a small amount of water and addition of several volumes of methanol, white crystals, m.p. 257–258° dec.

Anal. Calc'd for $C_9H_{20}N_2O_6S_2$: C, 34.2; H, 6.4; N, 8.9; SO_4-S, 10.1.

Found: C, 34.9; H, 6.7; N, 8.6; SO_4-S, 9.9.

2-(δ-Carboxybutyl)-5-ketoimidazolido[4,5,c,cis]thiophane (dl-biotin) (XXX). A clarified solution of 650 mg. of 2-(δ-carboxybutyl)-3,4-*cis*-diaminothiophane (XXIX) sulfate in 26 cc. of 10% potassium carbonate was treated with phosgene with shaking and ice cooling until acidic. The white crystals which separated were washed with ice-water, m.p. 223–224°; yield 450 mg. (90%). Recrystallization from 50% aqueous methanol gave long white needles, m.p. 226–228°, micro m.p. 230–232°. An assay with *Lactobacillus arabinosis* showed that this compound had 52% of the activity of natural biotin.

Anal. Calc'd for $C_{10}H_{16}N_2O_3S$: C, 49.2; H, 6.6; N, 11.5.

Found: C, 49.1; H, 6.7; N, 11.2.

The methyl ester formed white crystals from methanol-ether, micro m.p. 127–128°. After this work was completed Grüssner, Bourquin, and Schnider (12) recorded the m.p. 130° for this compound.

Anal. Calc'd for $C_{11}H_{18}N_2O_3S$: C, 51.2; H, 7.0.

Found: C, 51.5; H, 7.1.

Harris, *et al.* (5) give the m.p. of *dl*-biotin as 232°.

Resolution with *l*(+)-arginine (9) gave biotin, micro m.p. 231–232°, $[\alpha]^{25}_{D}$ +89.7° (c = 1.00 in 0.1 *N* sodium hydroxide). Admixture with natural biotin gave no depression in the melting point.

SUMMARY

Controlled isomer syntheses of *dl*-biotin and *dl*-*epi*allobiotin have been described.

The two rings of biotin and *epi*biotin have been established to have a *cis* configuration at the bridgehead whereas those of *epi*allobiotin and allobiotin are related *trans*.

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CONSTITUENTS OF PYRETHRUM FLOWERS. XX. THE PARTIAL SYNTHESIS OF PYRETHRINS AND CINERINS AND THEIR RELATIVE TOXICITIES

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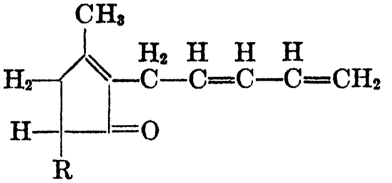
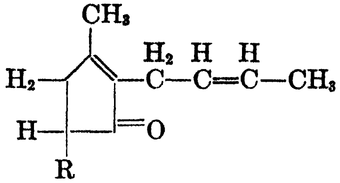
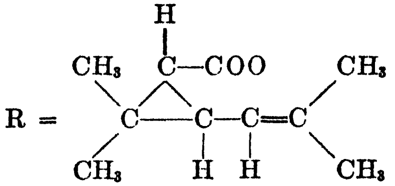
In the four preceding articles (1) it has been demonstrated that the methylcyclopentenolone esters of chrysanthemum monocarboxylic acid, previously designated as "pyrethrin I" and of monomethyl chrysanthemum dicarboxylic acid, designated as "pyrethrin II", consist not of homogeneous compounds but of mixtures of two constituents which differ from each other with respect to the nature of the side chain in the alcoholic-ketonic components.

These four constituents have now been designated as pyrethrins I and II (formula A) and cinerins I and II (formula B). Since the usual analytical methods are based on the determination of the respective acids, the results refer to the content of the mixture of pyrethrin I with cinerin I and that of pyrethrin II with cinerin II in the sample. The proportions of the constituents in these mixtures may vary with different conditions of culture or breed of plant or, since the pyrethrins are less stable than the cinerins and may be lost by polymerization

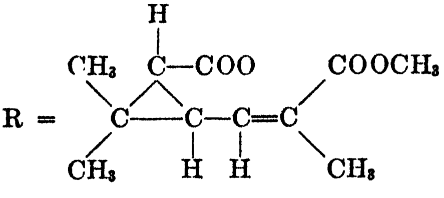

A


B

For pyrethrin I and cinerin I



For pyrethrin II and cinerin II



or oxidation, their proportions may be changed during the process of extraction or on subsequent treatment. As a consequence of the demonstration of the heterogeneous nature of the chrysanthemum acid esters and the establishment of the structure of their respective constituents, the importance of establishing their relative toxicities is from several standpoints at once evident.

If there should be a marked difference in insecticidal properties between the pyrethrins and the cinerins, the plant breeder should aim to increase the content of the more effective one. Discrepancies between analytical and biological results might sometimes be due to the relative proportions of pyrethrins and cinerins present. Also with a view to an eventual synthesis, it is apparent that in case the cinerins are equal to or approach the pyrethrins in value they will be less difficult to prepare. It is also of interest to attempt to determine the toxicological effects produced by various structural modifications. By pursuing this line of research, it would be possible to determine which features of this class of compounds are essential to insect toxicity and which are nonessential.

For these studies it was decided to compare the insecticidal properties of the pure pyrethrins and cinerins prepared by esterification of chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid monomethyl ester with pyrethrolone formula A and cinerolone formula B (R = OH). Since both the optically active and the racemic forms of these compounds were available, it could be established whether or not optical activity in the alcoholic component is essential or important.

The effect of the reduction of points of unsaturation in the acid and in the alcoholic component could be determined by comparison of the two types of hydrogenated pyrethrins and cinerins.

The esterifications were carried out by the reaction of the hydroxy ketones and the chrysanthemum acid chlorides in benzene solution in the presence of pyridine. The acids employed were the natural dextro forms obtained by saponification of the mixture of semicarbazones of the "pyrethrins" and isolated by familiar procedures (2).

A method for obtaining chrysanthemum dicarboxylic acid monomethyl ester previously recommended (3), which is based on the cleavage of a pyrethrin II concentrate by hydrogenation, was found to result in the dihydro compound, contrary to the statement of Staudinger and Ruzicka that the double bond in the natural acid is stable to hydrogenation (2a). The dihydro acid obtained by this method served for the preparation of isodihydropyrethrin II and isodihydrocinerin II. Dihydrochrysanthemum monocarboxylic acid was obtained by hydrogenation of the natural chrysanthemum monocarboxylic acid. Hence, the prefix "isodihydro" in the names of all the isodihydropyrethrins and isodihydrocinerins indicates that the acid component is saturated. Natural pyrethrolone and cinerolone are dextrorotatory, as are also chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid monomethyl ester, but the pyrethrins and cinerins obtained by synthesis from these are all levorotatory.[1] When the prefix "active" or "racemic" is employed it refers to the optical characteristic of the alcoholic component. Active pyrethrin I and active cinerin I furnished crystalline semicarbazones in moderately good yields. The semicarbazones of the corresponding inactive compounds did not crystallize and no crystalline derivative was obtained from pyrethrin II or cinerin II.

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[1] In previous articles (1b, 1c), $[\alpha]_D$ of the semicarbazones of acetylpyrethrolone and acetylcinerolone were reported as $+50°$ and $+49°$, respectively. The signs should read minus instead of plus.

TABLE I

Analytical and Physical Data for Pyrethrins and Cinerins

COMPOUND	CALC'D		FOUND		METHOXYL		REFRACTIVE INDEX $n_D^{25°}$	SPECIFIC ROTATION
	C	H	C	H	Calc'd	Found		
Cinerin I, active	75.94	8.86	75.35	8.45			1.5119	$[\alpha]_D^{28}$ −27.4
			76.05	8.63				
			75.42	8.75				
Cinerin I, racemic			75.56	8.65			1.5110	$[\alpha]_D^{27}$ −14.26
Pyrethrin I, active	76.83	8.53	75.83	8.47				$[\alpha]_D^{25}$ −26.3
			76.07	8.56				
Pyrethrin I, racemic								$[\alpha]_D^{25}$ −14.66
Cinerin II, active	70.00	7.78	69.90	8.09	8.61	8.35	1.5175	
Cinerin II, racemic			69.83	7.76		8.30	1.5181	
Pyrethrin II, active	70.97	7.53	69.72	7.59	8.33	8.82		
Pyrethrin II, racemic			71.67	7.54		8.13		
Isodihydrocinerin I, active	75.47	9.43	75.45	9.14			1.4983	
Isodihydropyrethrin I, active	76.36	9.09	76.00	9.10			1.5081	
Tetrahydropyrethrin I, active	75.90	9.63	75.19	9.27			1.4917	
Isodihydrocinerin II, active	69.61	8.29	68.69	8.11	8.56	8.44	1.4958	$[\alpha]_D^{28}$ −21.2
			68.72	8.20				
Isodihydropyrethrin II, active	70.58	8.02	70 65	7.37	8.27	8.62	1.5110	$[\alpha]_D^{28}$ −21.1
			69.78	7.62		8.32		
			68.25	7.85				
			68.84	7.94				
Isodihydropyrethrin II, racemic						8.43		$[\alpha]_D^{28}$ −10.5
Dihydrochrysanthemum dicarboxylic acid monomethyl ester	61.68	8.41	61.99	8.20	14.5	13.95		
			60.92	7.92		13.40		
						13.80		
Pyrethrin I semicarbazone active	68.57	8.05	67.46	7.75				
			67.78	8.10				

EXPERIMENTAL

The following examples will illustrate the procedure employed for obtaining the synthetic pyrethrins and cinerins.

Active pyrethrin I. One and seven-tenths grams of pyrethrolone (n_D^{25} 1.5433, $[\alpha]_D^{30}$ +11.7°) and 1.5 ml. of dry pyridine in 15 ml. of dry benzene were added to 2 g. of chrysanthemum monocarboxylic acid chloride in 15 ml. of benzene. The hydrochloride of pyridine separated in a short time, and the reaction mixture was allowed to stand for about 24 hours at room temperature. The crystalline material was filtered off, and the solution was extracted with water and sodium bicarbonate solution. After removal of the solvent in vacuum, the residue was transferred to a small distilling flask with acetone, and the solvent was removed by evaporation. The distillation flask consisted of a specially constructed bulb with an inclined delivery tube of large diameter located about 1 cm. above the bulb leading to a receiving bulb connected to the vacuum line. The boiling bulb was provided with a very fine capillary, and the distillation was carried out under a vacuum of about 0.1 mm. and a bath temperature of about 170°. The time of heating was in all cases very short.

The semicarbazone was prepared in pyridine-alcohol solution. After recrystallization from ether it melted at 75–80°.

Active cinerin I. One and seven-tenths grams of active cinerolone (n_D^{25} 1.5198 $[\alpha]_D^{25}$ +9.9°) in 15 ml. of benzene and 1.5 ml. of dry pyridine were added to 1.7 g. of chrysanthemum monocarboxylic acid chloride in 15 ml. of benzene. The reaction proceeded with separation of crystalline pyridine hydrochloride, and the product was treated in the same manner as described above.

The semicarbazone was prepared, and after recrystallization from ether melted at 67–70°.

Active pyrethrin II and cinerin II. The same conditions were observed as for pyrethrin I and cinerin I with substitution of methyl chrysanthemum dicarboxylic acid chloride (1.1 moles) for the monocarboxylic acid chloride. For the distillation of the ester a higher temperature was required and the oil-bath was heated to 200°. By the same procedure the following compounds were also prepared: Racemic pyrethrin I, racemic cinerin I, racemic pyrethrin II, racemic cinerin II, active isodihydropyrethrin I, active isodihydrocinerin I, active isodihydropyrethrin II, active isodihydrocinerin II, racemic isodihydropyrethrin II, active tetrahydropyrethrin I.

RELATIVE TOXICITIES OF PYRETHRINS AND CINERINS AND THEIR HYDROGENATED DERIVATIVES

Fourteen compounds were therefore made available for biological tests. The analytical data and physical constants for these compounds are presented in Table I.

The biological tests against houseflies, which were carried out by Gersdorff (4), gave results which may be briefly summarized as follows: Pyrethrin I is 1.5 times as toxic as cinerin I. Pyrethrin II is 1.3 times as toxic as cinerin II Pyrethrin I is 4.0 times as toxic as pyrethrin II. Cinerin I is 4.0 times as toxic as cinerin II. Pyrethrin I is 2.0 times as toxic as isodihydropyrethrin I. Cinerin I is 2.0 times as toxic as isodihydrocinerin I. Isodihydropyrethrin I is about 1.75 times as toxic as isodihydrocinerin I. Tetrahydropyrethrin I is less than 0.03 times as toxic as pyrethrin I. The toxicity in all cases was independent of the presence of optical activity in the alcoholic ketone components, *i.e.*, whether the compound had been prepared from dextro or racemic pyrethrolone or cinerolone.

BELTSVILLE, MD.

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[Contribution from Noyes Chemical Laboratory, University of Illinois]

SOME NITRO DERIVATIVES OF 2,4- AND 2,6-DIMETHYLQUINOLINE[1]

CHARLES C. PRICE,[2] BERNARD H. VELZEN,[3] AND DAVID B. GUTHRIE[4]

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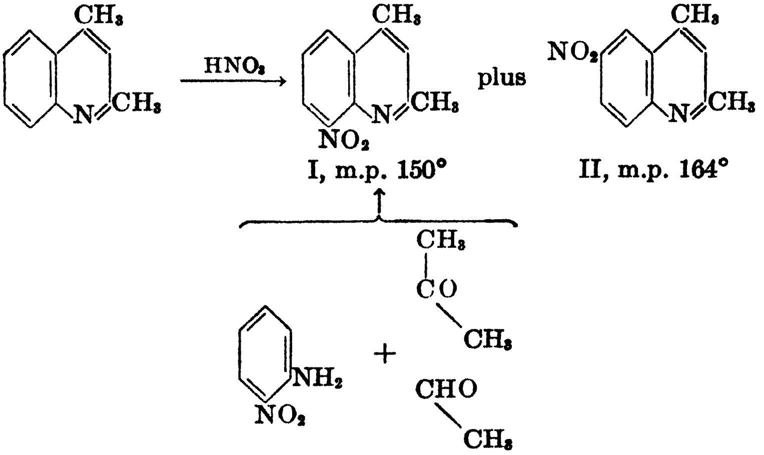
The high antimalarial activity of pamaquine (Plasmochin) suggested that other 8-aminoquinoline drugs be prepared for evaluation. The present paper describes some experimental observations which arose from the preparation of 2,4- and 2,6-dimethyl-8-nitroquinoline as intermediates for this purpose.

According to Roberts and Turner (1), 2,4-dimethylquinoline may be nitrated readily at low temperatures to produce a compound melting at 119°. This was assigned the structure of the 8-nitro derivative, since on reduction and diazotization it could be converted to 8-chloro-2,4-dimethylquinoline, identical with an authentic sample. Roberts and Turner (1) further reported the Baeyer synthesis on *o*- and *p*-nitroaniline to yield products, m.p. 145–147° and 159–162°, respectively, but stated that the former could not have been the expected 2,4-dimethyl-8-nitroquinoline.

When the nitration of 2,4-dimethylquinoline was carried out according to the directions of Roberts and Turner (1), a good yield of crude nitro derivatives was obtained. A small sample recrystallized from alcohol had the melting point (120°) reported by Roberts and Turner. However, a similar recrystallization of the bulk of the nitroquinoline yielded a material melting at 110–138°. Careful fractionation by dilute sulfuric acid extraction followed by recrystallization gave two pure dimethylnitroquinolines, m.p. 149–150° and 163–164°. These melting points correspond well with the products from the Baeyer synthesis carried out by Roberts and Turner (1). They therefore have been assigned the structure of 2,4-dimethyl-8- and -6-nitroquinoline, respectively.



I, m.p. 150°

II, m.p. 164°

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[1] The work reported herein was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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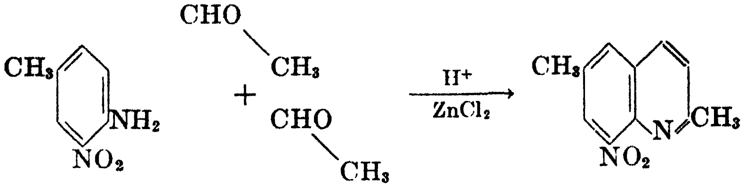
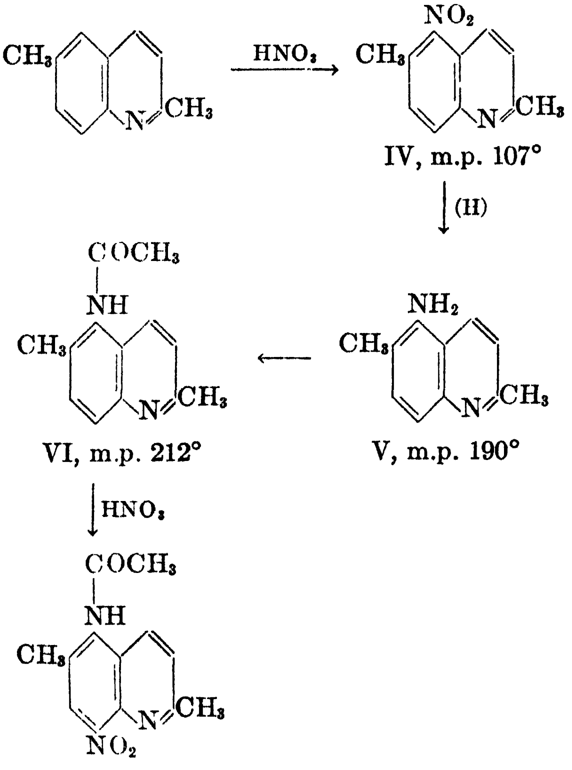
A diagram of the melting points of mixtures of these two substances (Fig. 1) indicates that the material obtained by Roberts and Turner was the eutectic mixture containing two moles of the 8-nitro derivative (I) to one of 6-nitro (II).

Early attempts to prepare 8-nitro-2,6-dimethylquinoline by the Doebner-von Miller reaction on 3-nitro-4-aminotoluene gave only about 1% yields (2). The modified procedure of Mills, Harris, and Lambourne (3) gave a 25% yield of the desired product, isolated as white crystals, m.p. 116–117°.



III, m.p. 117°

2,6-Dimethylquinoline was nitrated readily in good yield to form a substance (IV) not identical with the 8-nitro derivative (III). The nitro group probably entered the 5-position, although the possibility of the formation of the 7-isomer has not been excluded.



IV, m.p. 107°

V, m.p. 190°

VI, m.p. 212°

VII, m.p. 295°

EXPERIMENTAL[5]

Nitration of 2,4-dimethylquinoline. A solution of 204 g. of 2,4-dimethylquinoline [prepared in 88% yield according to the directions of Coombes (4)] in 1020 g. of concentrated sulfuric acid was cooled to 5° in an ice-bath. While this solution was stirred vigorously, a mixture of 193 g. of fuming nitric acid (*d.* 1.4) and 387 g. of concentrated sulfuric acid (*d.* 1.84) was added slowly, maintaining the temperature at 5±2°. The mixture was poured on ice, made alkaline with ammonium hydroxide, and filtered. There was collected 324 g. of a wet, brown solid, m.p. 90–110°. A small sample recrystallized from aqueous ethanol melted at 118–120°. Recrystallization of the major portion from an ethanol-water mixture gave 220 g. (84.3%) of a pale brown solid, m.p. 110–138°.

Five grams of this latter material was fractionally recrystallized from 100 cc. of 95% ethanol and 50 cc. of water. The warm mixture was treated with Darco, filtered, and then cooled. The first crop of crystals weighed 1.5 g., m.p. 144–147°. Each succeeding crop of crystals was obtained by evaporating the filtrate to one-half its volume and cooling. The last crop was obtained by diluting the filtrate with a large volume of water. The following crops were obtained.

Crop. No.	*Wt.*	*M.P.*
1	1.50	144–147°
2	1.40	117–147°
3	0.45	115–138°
4	0.59	79–84°
5	0.16	75–90°

The first crop was recrystallized twice from 50% ethanol giving white needles of *8-nitro-2,4-dimethylquinoline*, m.p. 149.5–150°.

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.86.
Found: C, 65.19; H, 5.01; N, 14.25.

The crude nitration mixture above (m.p. 90–110°) was repeatedly extracted with very dilute hot sulfuric acid until the insoluble residue melted at 139–143°. The 8-nitro derivative, with the nitro group *ortho* to the quinoline nitrogen would, of course, be expected to be less basic than the other isomers and thus less soluble in dilute acid. The acid-soluble fraction was precipitated and re-extracted. The second acid-soluble fraction, on recrystallization from aqueous acetone, melted at 162–164°. This material, *6-nitro-2,4-dimethylquinoline*, was sublimed for analysis, m.p. 163–164.°

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: N, 13.86. Found: N, 13.69.

Data on the melting points of mixtures of these two isomers are summarized in Fig. 1.

Preparation of 8-nitro-2,4-dimethylquinoline by the Baeyer reaction. A rapid stream of dry hydrogen chloride was passed into a vigorously-agitated mixture of 96 g. of paraldehyde and 160 g. of anhydrous acetone. After three hours the passage of gas was stopped; the mixture weighed 404 g. and was allowed to stand at room temperature for four days. *o*-Nitroaniline (35 g.) was thoroughly mixed by grinding with 62 cc. of concentrated hydrochloric acid and 14 g. of nitrobenzene was added. To this mixture was added 57 g. of the ethylideneacetone solution as prepared above and the whole was heated at 100° for ten hours.

The reaction mixture was extracted with three 200-cc. portions of ether. The water layer was made alkaline with sodium hydroxide and filtered. The solid material was dissolved in hot ethanol, enough water was added to make the solution cloudy and the mixture was then boiled with Darco. From the cooled filtrate, 5.5 g. of a yellow product was isolated, m.p. 145–147°. After one recrystallization from an ethanol-water mixture, it melted at 149–150°. A mixed melting point with the nitro compound obtained by fractional recrystallization (see above) showed no depression. This would seem to establish definitely the melting point of *8-nitro-2,4-dimethylquinoline* as 149.5–150°.

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[5] Analyses by Miss Theta Spoor and Mr. Harold Clark. All melting points are corrected.

8-Nitro-2,6-dimethylquinoline. The procedure employed was essentially that of Mills, Harris, and Lambourne (3). A mixture of 505 g. (3.32 moles) of 3-nitro-4-aminotoluene and 1128 cc. of concentrated hydrochloric acid was cooled in an ice-bath. To this mixture was added in small portions 365.2 g. (8.3 moles) of acetaldehyde dissolved in 91 cc. of water. After addition was completed, the mixture was kept cold for one-half hour and 270 g. (1.99 mole) of zinc chloride was added. The mixture was then boiled under reflux for four hours. The cooled reaction mixture was filtered and the filtrate made alkaline with sodium hydroxide. The brown-green precipitate was collected and taken up in ethanol and again filtered to remove zinc salts.

The boiling alcoholic filtrate was diluted just to cloudiness, treated with Darco and filtered. After a second treatment with Darco, the filtrate on cooling and further dilution with water gave 170 g. (25.4%) of *8-nitro-2,6-dimethylquinoline*, m.p. 114–115°. After two recrystallizations from an ethanol-water mixture, the colorless crystals melted at 116–117°.

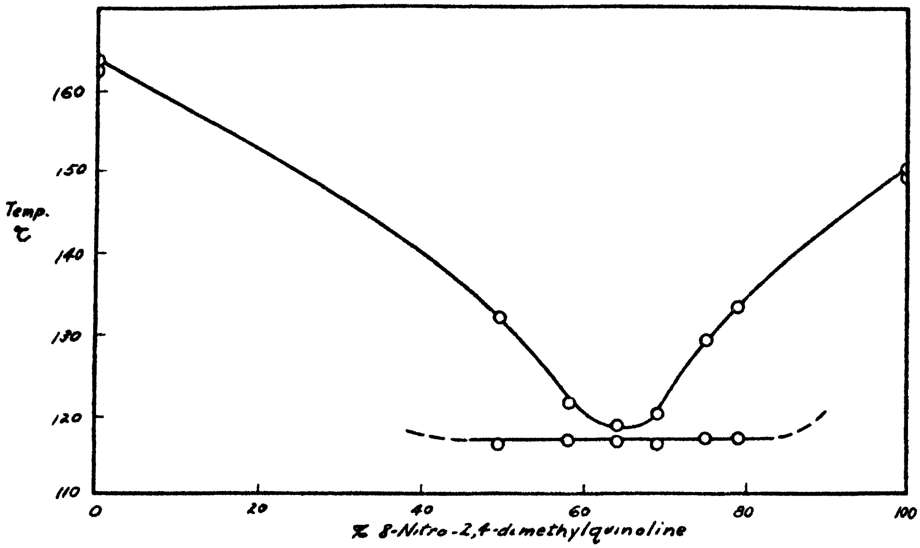

FIG. 1. MELTING POINT DIAGRAM FOR MIXTURES OF 6- AND 8-NITRO-2,4-DIMETHYLQUINOLINE

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.86.
Found: C, 65.21; H, 4.99; N, 14.20.

This material is apparently the same substance as that reported by Bartow and McCollum (2) as a red solid, m.p. 114°.

Nitration of 2,6-dimethylquinoline. A 25-g. sample of 2,6-dimethylquinoline (5) was dissolved in 125 cc. of concentrated sulfuric acid. To this stirred mixture, cooled to 5° in an ice-bath, was added slowly a mixture of 24 g. of fuming nitric acid (*d.* 1.5) and 48 g. of concentrated sulfuric acid (*d.* 1.84). Immediately after the addition was completed, the mixture was poured into a beaker containing ice and the solution was made alkaline with ammonium hydroxide. The pale yellow precipitate, m.p. 95–97°, was recrystallized from an ethanol-water mixture to give 28.0 g. (85.5%) of white needles, m.p. 104–107°. After two additional recrystallizations from alcohol, the product melted at 106–107°.

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.86.
Found: C, 65.15; H, 4.89; N, 14.06.

The most likely structure for this material would appear to be that of *5-nitro-2,6-di-*

methylquinoline. The investigation was terminated, however, before it was possible to establish the position of the nitro group.

5-Amino-2,6-dimethylquinoline. A mixture of 25 g. (0.123 mole) of the nitroquinoline and 250 cc. of 50% glacial acetic acid was warmed on a steam-bath. To the vigorously-agitated mixture, 20.7 g. (0.37 gram-atom) of iron (100 mesh) was added in small portions during a period of one and one-half hours. Heating was continued for thirty minutes after addition was completed. The mixture was made alkaline with sodium hydroxide and filtered. The collected precipitate, in a Soxhlet extractor, was extracted for forty-eight hours with 500 cc. of ethanol.

The ethanolic extract was concentrated to 100 cc. and enough water was added to make the boiling solution faintly cloudy. After treatment with Darco, the solution was filtered, cooled, and diluted with water, giving 18.4 g. (85.5%) of the amino compound, m.p. 189–189.5°. It was recrystallized twice from 50% ethanol as white needles, m.p. 189–189.5°.

Anal. Calc'd for $C_{11}H_{12}N_2$: C, 76.70; H, 7.03; N, 16.27.
Found: C, 76.65; H, 6.90; N, 16.45.

Acetylation in boiling acetic anhydride produced *5-acetamino-2,6-dimethylquinoline,* which crystallized from 50% ethanol as white needles, m.p. 211–212°.

Anal. Calc'd for $C_{13}H_{14}N_2O$: C, 72 67; H, 6.59.
Found: C, 72.73; H, 6.71.

8-Nitro-2-acetamino-2,6-dimethylquinoline. To 1 g. of 5-acetamino-2,6-dimethylquinoline in 5 cc. of concentrated sulfuric acid was added 1.5 cc. of fuming nitric acid in 1.5 cc. of concentrated sulfuric acid. The solution was allowed to come to room temperature, poured onto ice, and the precipitate was recrystallized several times from aqueous ethanol to yield *8-nitro-5-acetamino-2,6-dimethylquinoline* as long, colorless needles, m.p. 292–294° (aluminum block).

Anal. Calc'd for $C_{13}H_{13}N_3O_3$: C, 60 22; H, 5.05.
Found: C, 60.55; H, 5.01.

SUMMARY

It has been shown that the product, melting at 120°, obtained by nitration of 2,4-dimethylquinoline is not pure 8-nitro-2,4-dimethylquinoline as reported by Roberts and Turner but is the eutectic mixture of two parts of the 8-nitro derivative, m.p. 150°, and one of the 6-nitro derivative, m.p. 164°.

The nitration of 2,6-dimethylquinoline produced a compound not identical with the 8-nitro derivative and presumed to be 5-nitro-2,6-dimethylquinoline.

URBANA, ILL.

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[Contribution from the Purdue Research Foundation and the Department of Chemistry, Purdue University]

NITROALKENE-ANTHRANILIC ACID ADDITION PRODUCTS

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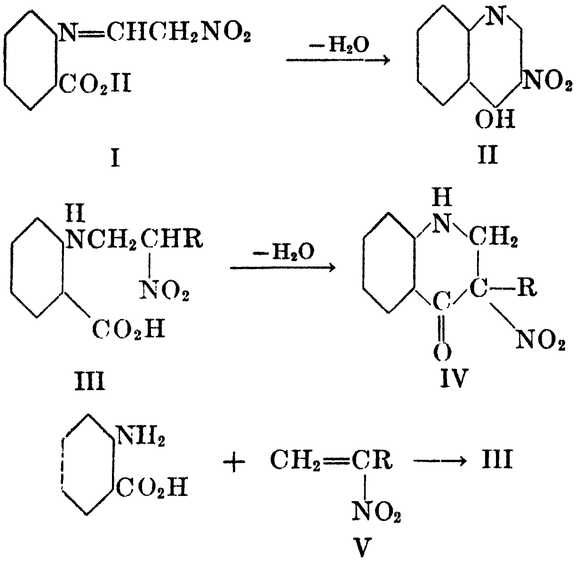
The long-known synthesis (1) of 3-nitro-4-hydroxyquinoline (II) by dehydration of 2-(2′-nitro-1′-ethylidenamino)benzoic acid (I) suggested that similar dehydrations of 2-(2′-nitro-1′-alkylamino)benzoic acids (III) might lead to the formation of 3-nitro-4-keto-1,2,3,4-tetrahydroquinolines (IV), valuable for synthetic purposes and of interest in antimalarial research.



We have found that compounds of type III are readily obtainable from the reactions of anthranilic acid with 2-nitro-1-alkenes (V). Initial experiments on this condensation were performed with anthranilic acid and 2-nitro-1-butene (V, R = C_2H_5). Condensation occurs readily on heating and yields 2-(2′-nitro-1′-butylamino)benzoic acid (III, R = C_2H_5). This synthesis was later modified in order that the more stable 2-nitro-1-butyl acetate could be substituted for 2-nitro-1-butene as a reagent. The former is readily decomposed to the latter by warm water or basic salts (2), and when this decomposition takes place in the presence of anthranilic acid the latter reacts with the 2-nitro-1-butene as it is formed to give good yields of the desired product. Another compound of this type, 2-(2′-nitro-1′-ethylamino)benzoic acid (III, R = H) was synthesized by a similar decomposition of 2-chloro-1-nitroethane (3) in the presence of sodium anthranilate. Attempts to extend the synthesis to include secondary nitroalkenes such as 2-nitro-2-butene and 4-nitro-3-heptene or the acetates of the corresponding nitro alcohols were unsuccessful.

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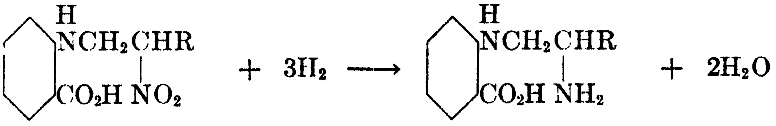
The 2-(2′-nitro-1′-alkylamino)benzoic acids (III) are insoluble in water and dilute acids but soluble in concentrated mineral acids and may be quantitatively recovered from the latter solutions by dilution with water. On the other hand, they are very unstable toward alkali, and solutions of their ammonium or sodium salts rapidly decompose to regenerate the original nitroalkene and salts of anthranilic acid.

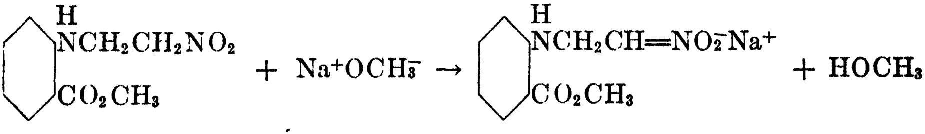
All attempts to cyclize the 2-(2′-nitro-1′-alkylamino)benzoic acids to the corresponding tetrahydroquinoline derivatives were unsuccessful. Refluxing with acetic anhydride and sodium acetate causes extensive decomposition and at lower temperatures the only reaction is acetylation of the aminoid nitrogen; this derivative was isolated in the case of 2-(2′-nitro-1′-butylamino)benzoic acid. Concentrated sulfuric or phosphoric acids fail to cause any change at 150°, and the compounds may be quantitatively recovered by dilution with water. Thionyl chloride and the phosphoric halides react vigorously with the nitro acids, III, presumably converting them to the corresponding acid chlorides. However, no cyclization occurs and the original nitro acids are regenerated on dilution with water. Treatment of the acid chlorides with alkali, pyridine, or anhydrous aluminum chloride also fails to cause cyclization.

Both of the nitro acids were subjected to catalytic hydrogenation in the hope that simultaneous reduction and cyclization might occur, but only the corresponding amino acids (VI) were obtained.



VI

Attempts to cyclize the methyl ester (VII) of the aforementioned 2-(2′-nitro-1′-ethylamino)benzoic acid by aqueous alkali and by sodium methoxide in methanol result only in the same type of decomposition noted with the acid itself. Methanol-free sodium methoxide in absolute ether gives a precipitate of the sodium salt of the nitronic acid (VIII) which is unchanged after 48 hours refluxing in ether.



VII VIII

It is difficult to understand the resistance of the 2-(2′-nitro-1′-alkylamino) benzoic acids (III) to cyclization in view of the ease with which 2-(2′-nitro-1′-ethylidenamino)benzoic acid (I) is cyclized. Although the —N═CH- grouping in I undoubtedly acts as a powerful activator for the methylenic hydrogens, those of III are sufficiently labile to form a sodium derivative in nonpolar solvents. Further investigation of this phenomenon is indicated.

Acknowledgment. The authors are indebted to Eli Lilly and Company, Indianapolis, Indiana, and to the Purdue Research Foundation for the funds which supported this work.

EXPERIMENTAL

All melting points are corrected.

2-(2'-Nitro-1'-butylamino)benzoic acid (III, R = C_2H_5). A mixture of 32.2 g. (0.20 mole) of 2-nitro-1-butyl acetate (2), 13.2 g. (0.22 mole) of glacial acetic acid, 35 ml. of water, 30.1 g. (0.22 mole) of anthranilic acid, and 16.4 g. (0.20 mole) of sodium acetate was stirred continuously and heated at 90–95° for one hour, then allowed to cool to room temperature. The crystalline product (41 g. of crude, m.p. 138–140°) was filtered off, washed with water and dried at 60°. It was dissolved in hot benzene, boiled with charcoal, filtered through a preheated funnel and cooled slowly to 15–20°. The product was filtered off, rinsed with benzene, and dried at 60°; yield 34–37 g. (71–78%) of pale tan needles, m.p. 142–143°. Repeated crystallization and decolorization failed to remove the faint color or change the melting point.

Anal. Calc'd for $C_{11}H_{14}N_2O_4$: C, 55.44; H, 5.92; N, 11.76; neut. equiv., 238.1.

Found: C, 55.45, 55.48; H, 5.91, 6.02; N, 11.75, 11.86; neut. equiv., 238.0, 238.1.

2-(2'-Nitro-1'-ethylamino)benzoic acid (III, R = H). A solution of 8.1 g. (0.059 mole) of anthranilic acid in 25 ml. of methanol was stirred with 5.0 g. (0.06 mole) of sodium bicarbonate and 15 ml. of water, warmed until the evolution of carbon dioxide was complete, and cooled to room temperature. Then 5.9 g. (0.053 mole) of 2-chloro-1-nitroethane (3) was added and the mixture was stirred for 30 minutes. It was then diluted with 200 ml. of hot water, allowed to cool to room temperature, and finally filtered; yield 10.9 g. of crude product, m.p. 150–151°. Recrystallization from 300–350 ml. of benzene gave 10.0 g. (90%) of white crystals, m.p. 155–156°.

Anal. Calc'd for $C_9H_{10}N_2O_4$: C, 51.40; H, 4.81; N, 13.33.

Found: C, 51.45, 51.54; H, 4.87, 4.91; N, 13.39, 13.47.

Methyl 2-(2'-nitro-1'-ethylamino)benzoate (VII). A solution of 3.8 g. (0.025 mole) of methyl anthranilate, 2.7 g. (0.025 mole) of 2-chloro-1-nitroethane, and 2.5 ml. (0.03 mole) of pyridine in 10 ml. of methanol (99–100%) was refluxed for 90 minutes. The solution was then diluted with 50 ml. of water and allowed to cool to room temperature. The product was filtered off, washed with water, and dried at room temperature; yield 5.4 g. of crude material, m.p. 70–75°. It was recrystallized from 125 ml. of ligroin, (b.p. 90–100°) giving 4.1 g. (73%) of pale yellow needles, m.p. 84°. Several recrystallizations from ligroin gave a white product but no change in m.p.

Anal. Calc'd for $C_{10}H_{12}N_2O_4$: C, 53.55; H, 5.40; N, 12.50.

Found: C, 53.58, 53.59; H, 5.37, 5.42; N, 12.57, 12.60.

2-N-(2'-nitro-1'-butyl)acetylaminobenzoic acid. A mixture of 6.0 g. (0.025 mole) of 2-(2'-nitro-1'-butylamino)benzoic acid and 15 ml. of acetic anhydride was stirred while 2.0 g. (0.025 mole) of anhydrous sodium acetate was added. When the spontaneous reaction subsided the mixture was stirred and heated to 80°, then allowed to cool. It was diluted with 50 ml. of water and neutralized with solid potassium carbonate, then acidified with excess concentrated hydrochloric acid. The precipitated oil was extracted with ether, which was then carefully evaporated. The residue was mixed with water and allowed to crystallize; yield 3.5 g. (50%) of white crystals, m.p. 119–120° (decomp.). Recrystallization from a mixture of benzene and ligroin gave white needles with the same m.p.

Anal. Calc'd for $C_{13}H_{16}N_2O_5$: C, 55.69; H, 5.75; N, 10.00.

Found: C, 55.77, 55.80; H, 5.74, 5.68; N, 10.01, 10.09.

2-(2'-Amino-1'-butylamino)benzoic acid (VI, R = C_2H_5). A mixture of 6.0 g. (0.025 mole) of 2-(2′-nitro-1′-butylamino)benzoic acid and Raney nickel catalyst in 75 ml. of 67% alcohol was shaken under hydrogen at an initial pressure of 4 atm. until the absorption of hydrogen ceased. The solution was warmed, filtered, then boiled with charcoal, filtered again, evaporated to incipient crystallization at the boiling point, and finally diluted with an equal volume of hot alcohol. After standing overnight the product was filtered off and dried at 100°; yield 3.8 g. (73%) of a faintly pink powder, m.p. 221–223° (decomp.). Recrystallization from water caused no change in m.p.

Anal. Calc'd for $C_{11}H_{16}N_2O_2$: C, 63.43: H, 7.74; N, 13.46.
Found: C, 63.47, 63.48; H, 7.71, 7.62; N, 13.54, 13.63.

2-(2′-Amino-1′-ethylamino)benzoic acid (VI, R = H). A mixture of 2.1 g. (0.01 mole) of 2-(2′-nitro-1′-ethylamino)benzoic acid, 125 ml. of water, and Raney nickel catalyst was shaken under hydrogen at an initial pressure of 4 atm. until the absorption of hydrogen ceased. The catalyst was filtered off, the filtrate was boiled with charcoal, filtered, evaporated to incipient crystallization and diluted with equal volume of alcohol. After standing overnight the product was filtered off, washed with alcohol, and dried at 100°; yield 1.4 g. (78%) of white crystals which slowly darkened, and melted about 220–225° (decomp.).

Anal. Calc'd for $C_9H_{12}N_2O_2 \cdot 1/3H_2O$: C, 58.06; H, 6.86; N, 15.05.
Found: C, 58.06, 58.13; H, 6.81, 6.92; N, 15.04, 15.14.

SUMMARY

1. The reactions of anthranilic acid with 2-nitro-1-alkenes and their derivatives are described.
2. The character of the products and a number of their reactions are discussed.

LAFAYETTE, IND.

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[Contribution from the Chemical Laboratory of the Academy of Commerce]

THE ACTION OF BENZENE AND ALUMINUM CHLORIDE ON TETRAHALOGENATED PHENOLS

MORITZ KOHN[1] AND S. REICHMANN

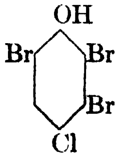
Received May 20, 1946

A considerable time ago, one of us, in collaboration with N. L. Müller (1), reported that the action of benzene and aluminum chloride on tribromophenol resulted in phenol and bromobenzene. Subsequently various halogenated phenols (2) were subjected to the same reaction. Of the tetrahalogenated phenols, only tetrabromophenol was available as starting material. Tetrabromophenol gave, with benzene and aluminum chloride, 3-bromophenol (3) and bromobenzene. Since then a number of new tetrahalogenated phenols have been prepared in the Vienna laboratory, and it seemed to us worth while to fill in the gaps by investigation of the action of benzene and aluminum chloride on these tetrahalogenated phenols.

All of the facts so far assembled in the study of this reaction with halogenated phenols have shown that the bromines ortho and para to the hydroxyl are replaced by hydrogen, while chlorine atoms are entirely unaffected, and that no rearrangements take place. The following results confirm these observations.

2,3,6-Tribromo-4-chlorophenol (I) (4), with benzene and aluminum chloride, yields a bromochlorophenol which by its mode of formation should be 3-bromo-4-chlorophenol (II).

3,4-Dibromo-2,6-dichlorophenol (III) (5) yielded a bromodichlorophenol, which similarly should be 3-bromo-2,6-dichlorophenol (IV).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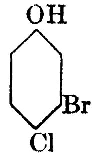
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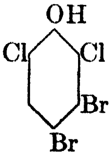
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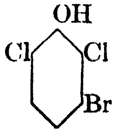
IV

The tribromo-2-chlorophenol (6) which was prepared from 2-chlorophenol in the Vienna laboratory might be, as was remarked at that time, either 3,4,6-tribromo-2-chlorophenol (V), or 4,5,6-tribromo-2-chlorophenol (VI). It seems probable that it is the latter (VI), but this must be offered with reservation, for a final decision must await further investigation. From the tribromo-2-chlorophenol (VI), a bromochlorophenol was obtained which should be 5-bromo-2-chlorophenol (VII). From V, 3-bromo-2-chlorophenol (VIII) would have been formed.

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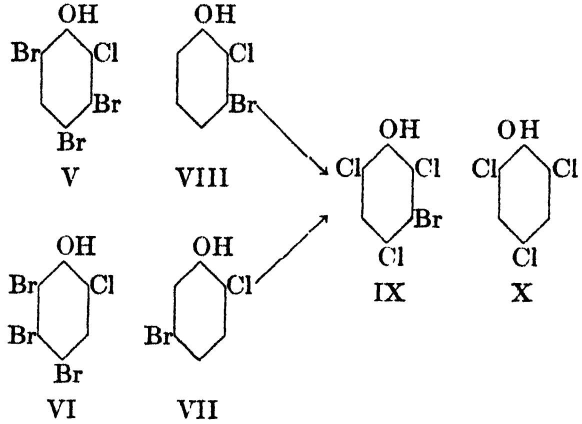

The three debromination products (II, IV, VII) were chlorinated. If the structures we have assumed are correct, all three must yield the same 3-bromo-2,4,6-trichlorophenol (IX); from VIII, IX would also be formed. The three compounds actually did give the same product, of the composition of a bromotrichlorophenol, and having the m.p. 74°. 3-Bromo-2,4,6-trichlorophenol has already been prepared in our laboratory (7) and described as melting at 76°. For this substance, unequivocal structural proof was obtained, since on reduction with zinc dust and acetic acid it gave 2,4,6-trichlorophenol (X) (8) by replacement of the *m*-bromine by hydrogen. Hamilton and Combie (9), who prepared bromotrichlorophenol from 3-bromoaniline, gave the m.p. 61°. Since we have prepared 3-bromo-2,4,6-trichlorophenol of m.p. 74–76° in four different ways, we must regard this m.p. as the correct one. Beyond melting point, we have completed the identification by preparation of derivatives (methyl ether, benzoyl ester). The formation of 3-bromo-2,4,6-trichlorophenol by chlorination of all three debromination products proves that in the debromination of I, III, and VI the bromine meta to the hydroxyl is unaffected, and that chlorine does not enter in the meta position.

EXPERIMENTAL[2]

The yields obtained in the debromination of tetrahalogenated phenols with benzene and aluminum chloride were approximately the same as those found by Kohn and Fink (3) in debromination of tetrabromophenol (40–50%). As has been mentioned (1), the yields depend upon the consistency of the aluminum chloride.

3-Bromo-4-chlorophenol (II) from 2,3,6-tribromo-4-chlorophenol (I). Finely powdered, well dried 2,3,6-tribromo-4-chlorophenol (120 g.) (4) was treated with 300 g. of anhydrous benzene and 250 g. of powdered anhydrous aluminum chloride, and refluxed with frequent shaking for 2 hours. The cooled, brown mixture was poured in small portions onto ice, and acidified with conc'd HCl. It was extracted with ether, dried (Na_2SO_4), and the residue from the ether distilled, giving successively benzene, bromobenzene, a phenolic fraction, and at 258–264°/748 mm. 3-bromo-4-chlorophenol (II), which immediately crystallized. It was crystallized from ligroin and washed with petroleum ether; white needles, m.p. 60°.

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[2] All boiling points are uncorrected.

Anal. Calc'd for C_6H_4BrClO: C, 34.71; H, 1.94.

Found: C, 34.47; H, 1.76.

3-Bromo-4-chloroanisole. This was prepared in the usual way with KOH and dimethyl sulfate on the water-bath, extracted with ether, and distilled at 242–248°/756 mm.

Anal. Calc'd for C_7H_6BrClO: OCH_3, 14.01. Found: OCH_3, 14.36.

Benzoyl derivative of 3-bromo-4-chlorophenol. This was prepared by the action of benzoyl chloride on an alkaline solution of the phenol in the usual way. The oil crystallized after 2 hours, was sucked dry, washed with water, and crystallized from alcohol; white needles, m.p. 100.5°.

Anal. Calc'd for $C_{13}H_8BrClO_2$: C, 50.09; H, 2.58.

Found: C, 50.23, 50.03; H, 2.84, 2.53.

3-Bromo-2,4,6-trichlorophenol (IX) from 3-bromo-4-chlorophenol (II). 3-Bromo-4-chlorophenol (6 g.) was dissolved with warming in 45 cc. of gl. acetic acid and chlorinated cold with exactly 2 moles of chlorine diluted with CO_2. A portion separated oily; the mixture was poured into a large volume of water with stirring, allowed to stand, and the precipitate filtered and crystallized from dilute acetic acid; white needles, m.p. 74°. Kohn and Rabinowitsch (7) give m.p. 76°.

Anal. Calc'd for $C_6H_2BrCl_3O$: C, 26.06; H, 0.73; AgCl + AgBr from 301.5 mg., 674.1 mg.

Found: C, 26.18; H, 1.36; AgCl + AgBr (Baubigny and Chavanne), 666.4 mg.

The bromotrichlorophenol was methylated with KOH and dimethyl sulfate, the solidified methyl ether sucked dry, dried in a vacuum over H_2SO_4, and distilled at 285–288°/753 mm. The solidified distillate was crystallized from dil. alcohol; white glistening needles of m.p. 63° [K. and R. (7), 65°].

Anal Calc'd for $C_7H_4BrCl_3O$: C, 28.93; H, 1.38.

Found: C, 29.34; H, 1.67.

3-Bromo-2,6-dichlorophenol (IV) from 3,4-dibromo-2,6-dichlorophenol (III). Dry 3,4-dibromo-2,6-dichlorophenol (60 g.) (5) with 160 g. of anhydrous benzene and 125 g. of aluminum chloride was refluxed for 3 hours, poured onto ice, acidified with conc'd HCl, and extracted with ether. Distillation of the ether residue gave benzene, bromobenzene, and finally in good yield a fraction at 264–270°/751 mm. which solidified immediately; from ligroin, white needles, m.p. 76.5°.

Anal. Calc'd for $C_6H_3BrCl_2O$. C, 29.77; H, 1.25; AgCl + AgBr from 235.8 mg., 462.6 mg.

Found. C, 29.47; H, 1.15; AgCl + AgBr, 466.6 mg.

3-Bromo-2,6-dichloroanisole. This was prepared in the usual way with KOH and dimethyl sulfate, b.p. 260–265°/750 mm.

Anal. Calc'd for $C_7H_5BrCl_2O$: OCH_3, 12.12. Found: OCH_3, 12.38.

Benzoyl derivative of 3-bromo-2,6-dichlorophenol. The benzoyl derivative, prepared in the usual way, crystallized from dil. alcohol in white needles of m.p. 102°.

Anal. Calc'd for $C_{13}H_7BrCl_2O$,: C, 45.1; H, 2.04.

Found; C, 44.85; H, 1.87.

3-Bromo-2,4,6-trichlorophenol (IX) from 3-bromo-2,6-dichlorophenol (IV). The chlorination of IV with one mole of chlorine was carried out as described above. The crude product crystallized from dil. acetic acid in white needles, m.p. 74°.

Anal. Calc'd for $C_6H_2BrCl_3O$: C, 26.06; H, 0.73.

Found: C, 26.11; H, 0.7.

The methyl ether prepared from this substance boiled at 284–286°/747 mm.; from dilute alcohol, white needles of m.p. 63°.

5-Bromo-2-chlorophenol (VII) from 4,5,6-tribromo-2-chlorophenol (VI). Dry VI (6) (120 g.) with 300 g. of benzene and 250 g. of aluminum chloride was debrominated by refluxing two hours, and worked up like the other examples. By distillation were obtained benzene, bromobenzene, a low-boiling phenolic fraction, and at 230–234°/744 mm. 5-bromo-2-chlorophenol, which crystallized from petroleum ether in white needles, m.p. 51°.

Anal. Calc'd for C_6H_4BrClO: AgCl + AgBr from 261.8 mg., 417.9 mg.

Found: AgCl + AgBr, 410.6 mg.

5-Bromo-2-chloroanisole distilled without decomposition at 240–245°/748 mm.

Anal. Calc'd for C_7H_6BrClO: OCH_3, 14.01. Found: OCH_3, 14.20.

3-Bromo-2,4,6-trichlorophenol (IX) from 5-bromo-2-chlorophenol (VII). 5-Bromo-2-chlorophenol was treated with two moles of chlorine as described above. The crude product, crystallized from dil. acetic acid gave white needles, m.p. 74°.

Anal. Calc'd for $C_6H_2BrCl_3O$: AgCl + AgBr from 285.2 mg., 632.7 mg.
Found: AgCl + AgBr, 630.9 mg.

The benzoyl derivative of this substance gave crystals from alcohol of m.p. 117°, in agreement with Kohn and Rabinowitsch (7).

SUMMARY

1. Three tetrahalogenated phenols have been subjected to debromination with benzene and aluminum chloride. With all three, bromobenzene was formed, with replacement of the bromines ortho and para to the hydroxyl by hydrogen. 2,3,6-Tribromo-4-chlorophenol gave 3-bromo-4-chlorophenol; 3,4-dibromo-2,6-dichlorophenol gave 3-bromo-2,6-dichlorophenol; 4,5,6-tribromo-2-chlorophenol gave 2-chloro-5-bromophenol.

2. The three debromination products all gave the same 3-bromo-2,4,6-trichlorophenol.

VIENNA, AUSTRIA

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[CONTRIBUTION FROM THE INSTITUTO DE FISIOLOGÍA, FACULTAD DE CIENCIAS MÉDICAS, AND THE LABORATORIO DE QUÍMICA ORGÁNICA, FACULTAD DE CIENCIAS EXACTAS, FÍSICAS Y NATURALES]

STUDIES ON ARGENTINE PLANTS. VIII. ON THE CONSTITUTION OF α-FAGARINE

V. DEULOFEU, R. LABRIOLA, AND B. BERINZAGHI

Received July 23, 1946

Of the three major alkaloids isolated by Stuckert (1) from the leaves and young twigs of *Fagara coco* (Gill) Engl., β-fagarine was identified by Deulofeu, Labriola, and De Langhe (2) as identical with skimmianine, and γ-fagarine as a methoxydictamine. Subsequent work by Berinzaghi, Muruzabal, Labriola, and Deulofeu showed that the methoxyl group is in position 8 of the nucleus (3).

α-Fagarine was described by Stuckert (1) as a base melting at 169° of formula $C_{19}H_{22}NO_4$, and was supposed to be identical with a base melting at 163° of formula $C_{19}H_{23}NO_5$ and named Fagarine I, which was isolated by Merck and Co. (Darmstadt, Germany), who carried out a large-scale preparation of the alkaloids of *Fagara coco* at Stuckert's request.

α-Fagarine has the very important pharmacological property of having a higher activity than quinidine in auricular flutter and auricular fibrillation (4).

In our first paper on the *Fagara coco* alkaloids (2), we proposed for α-fagarine the formula $C_{18}H_{21}NO_4$. It possesses two methoxyl groups, one dioxymethylene group, and one methylimino group. Further work has resulted in the preparation of a series of derivatives of this base, whose analyses agree, with the exception of the free base and the hydrochloride, with formula $C_{19}H_{23}NO_4$ that we accept in this paper as representing α-fagarine.

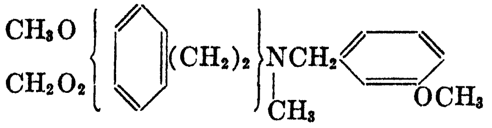
This base has very different properties from the other alkaloids of *Fagara coco*. α-Fagarine can be liberated from its salts only at *p*H 9. It is a tertiary base, does not react with nitrous acid, gives a methiodide, and a series of salts has been prepared. The existence of a dioxymethylene group has been confirmed, as the alkaloid gives a strong Labat's (5) test.

Fagarine can be distilled in a high vacuum without decomposition. It resists reduction by hydrogen at 4 atmospheres with Adams' platinum oxide catalyst and is recovered after treatment with ethanolic sodium hydroxide, with sodium ethoxide, or dilute hydrochloric acid. Heated with soda-lime, it yields methylamine.

Fagarine is oxidized by potassium permanganate in alkaline solution but no crystalline products could be isolated. In acid solution *m*-methoxybenzaldehyde and methanal were produced. Both were isolated and identified as 2,4-dinitrophenylhydrazones.

The production of *m*-methoxybenzaldehyde by oxidation can be interpreted as arising from a group $—CH_2C_6H_4OCH_3$ attached to the nitrogen atom, as no aliphatic double bond appears to be present in the molecule, and the lack of rotatory power excludes the existence of a series of cyclic structures. It follows that the remaining methoxyl and dioxymethylene groups are attached to another benzene ring.

Fagarine could be represented by the provisional structure:



which explains basicity, production of *m*-methoxybenzaldehyde, and lack of rotatory power, and although one is tempted to assign to it the structure of a substituted methylbenzylphenetylamine, further work is necessary to elucidate it in a complete form.

EXPERIMENTAL

The α-fagarine employed in this work was prepared by the acid extraction method described by us (2). Crude α-fagarine is best purified by one crystallization from acetone and recrystallization from ethanol (96%); well dried, it melts at 169–170°. The form with lower melting point described in our former papers contains solvent. Further purification can be carried out by distillation in a high vacuum (0.001 mm.) and at a bath temperature of 170–175°. Melting point of the distilled base, 169–170°.

For analysis, samples dried at constant weight were used (2 mm. vacuum and 120° for five hours).

Anal. Calc'd for $C_{19}H_{23}NO_4$: C, 69.30; H, 6.98; N, 4.25; M. W., 329.

Found: C, 68.39, 68.64; H, 6.26, 6.31; N, 4.33, 4.28; M. W. (11.6 mg. in 107.85 mg. camphor Δ, −13.5°), 321.

Dioxymethylene group. Two cubic centimeters of concentrated sulfuric acid was placed in a porcelain dish and 0.1 cc. of 5% ethanolic solution of α-fagarine and 0.1 cc. of 5% gallic acid solution added, and heated in a boiling water-bath. A green color developed that changed to blue. Piperonal was used as a positive control.

Tentative hydrogenation. Two hundred milligrams of base was shaken for two hours at 4 atmospheres pressure, with 50 mg. of Adams' platinum oxide. The base melting at 169–170° was recovered.

Action of alkalies. A small amount of α-fagarine was heated for 6 hours with 5% ethanolic solution of sodium hydroxide at 120°. The base melting at 169° was recovered.

The alkaloid was also recovered when boiled for one hour with absolute ethanol containing 2.5% dissolved sodium.

Action of hydrochloric acid. A small amount of α-fagarine was boiled for 3 hours with dilute hydrochloric acid (1:10) and recovered unchanged.

Hydrochloride. Three hundred milligrams of α-fagarine was suspended in 300 cc. of absolute ethanol and 0.1 cc. of concentrated hydrochloric acid added. The base dissolved, but immediately the hydrochloride crystallized out. Ether was added to complete crystallization and the solid hydrochloride filtered. After recrystallization from 96% ethanol, long prisms melting at 192–193° were obtained.

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot HCl + 0.5\ H_2O$: C, 60.80; H, 6.66.

Found: C, 60.95; H, 6.59.

Hydrobromide. To 500 mg. of α-fagarine suspended in 1.5 cc. of absolute ethanol, 0.5 cc. of hydrobromic acid (*d.* 1.38) was added. The base dissolved, ether was added to permanent turbidity, and the solution was kept cold until the hydrobromide crystallized out. It was recrystallized from 96% ethanol; long prisms melting at 186–188° (decomp.).

Anal Calc'd for $C_{19}H_{23}NO_4 \cdot HBr$: C, 55.61; H, 5.85.

Found: C, 55.59; H, 6.20.

Hydriodide. Two hundred twenty-five milligrams of sodium iodide was dissolved in 2 cc. of absolute ethanol, 90 mg. of acetic acid added, and then 330 mg. of α-fagarine. The base dissolved, and after standing, the hydriodide crystallized out. After recrystallization from absolute ethanol, it was obtained as long prisms melting at 190–192° (decomp.).

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot HI$: C, 49.89; H, 5.25.
Found: C, 49.63; H, 5.30.

Picrate. Three hundred milligrams of α-fagarine dissolved in 5 cc. of absolute ethanol was mixed with 300 mg. of picric acid in 5 cc. of absolute ethanol. The picrate crystallized immediately; by recrystallization from the same solvent, yellow plates melting at 208–209° were obtained.

Anal. Calc'd for $C_{19}H_{23}NO_4 \cdot C_6H_3N_3O_7$: C, 53.76; H, 4.65; N, 10.03.
Found: C, 53.95; H, 4.42; N, 9.82.

Methiodide. Five hundred milligrams of α-fagarine was boiled for three hours with 3 cc. of methyl iodide in 10 cc. of acetone. The methiodide crystallized, and was purified from 96% ethanol; long needles melting at 205° (decomp.).

Anal. Calc'd for $C_{20}H_{26}INO_4$: C, 50.95; H, 5.52.
Found: C, 50.93; H, 5.58.

Oxidation. Characterization of m-methoxybenzaldehyde. Five hundred milligrams of α-fagarine was dissolved in 30 cc. of dilute sulfuric acid (1:1) and at room temperature a solution of 1.3 g. of potassium permanganate in water added slowly. The permanganate was decolorized immediately. When the addition was finished, the resulting solution was distilled with steam and the distillate extracted with ether. On evaporation, the ether left a residue that, treated with a hydrochloric acid solution of 2,4-dinitrophenylhydrazine, gave a crystalline orange precipitate melting at 210°. After recrystallization from acetic acid it melted at 220° and no depression was obtained with an authentic sample of *m*-methoxybenzaldehyde 2,4-dinitrophenylhydrazone that also melted at 220°.

Anal. Calc'd for $C_{14}H_{12}N_4O_5$: C, 53.16; H, 3.79.
Found: C, 53.01; H, 4.00.

Characterization of methanal. By adding a hydrochloric acid solution of 2,4-dinitrophenylhydrazine to the water solution left after the *m*-methoxybenzaldehyde had been extracted with ether, a yellow crystalline precipitate was obtained, which after crystallization from ethanol melted at 165–166° and gave no depression with a pure sample of methanal dinitrophenylhydrazone.

Anal. Calc'd for $C_7H_6N_4O_4$: N, 26.66. Found: N, 26.36.

Action of soda-lime. Characterization of methylamine. Five hundred milligrams of α-fagarine was mixed with an excess of soda-lime and slowly heated. The gases were collected in dilute hydrochloric acid (1:10) and the heating was stopped when no more gases were evolved.

The acid solution was extracted with ether, alkalified, and distilled, collecting the distillate in an ethanolic solution of 2,4-dinitrochlorobenzene (6). On standing, a precipitate appeared, which after recrystallization from ethanol melted at 176°, and gave no depression with a pure sample of 2,4-dinitromethylaniline.

SUMMARY

1. α-Fagarine, one of the major alkaloids of *Fagara coco* (Gill) Engl. has been characterized as a tertiary base and a series of derivatives prepared.
2. Oxidation of α-fagarine with potassium permanganate in acid medium has yielded *m*-methoxybenzaldehyde and methanal.
3. A preliminary structure for α-fagarine is proposed.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

OXIMES OF DIALKYLAMINOBUTANEDIONES

G. BRYANT BACHMAN AND D. E. WELTON[1]

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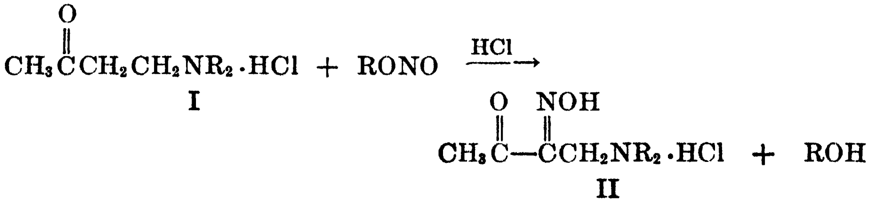
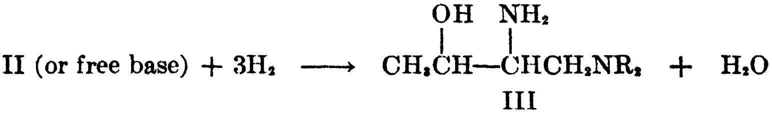
A variety of β-dialkylamino ketones have been prepared from ketones by means of the Mannich reaction (1). Nitrosation of these β-dialkylamino ketones (reaction A) followed by hydrogenation of the resultant dialkylamino-oximido ketones (reaction B) appeared to furnish a ready approach to the synthesis of a series of dialkylaminohydroxyalkylamines. We have investigated the application of these reactions to the hydrochlorides of 1-diethylamino-3-butanone (I, R = C_2H_5) (2) and 1-(N-piperidine)-3-butanone (I, R_2 = C_5H_{10}) (3).

A.



$$\underset{\text{I}}{\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2NR_2\cdot HCl}} + \mathrm{RONO} \xrightarrow{\mathrm{HCl}} \underset{\text{II}}{\mathrm{CH_3\overset{\overset{O}{\|}}{C}-\overset{\overset{NOH}{\|}}{C}CH_2NR_2\cdot HCl}} + \mathrm{ROH}$$

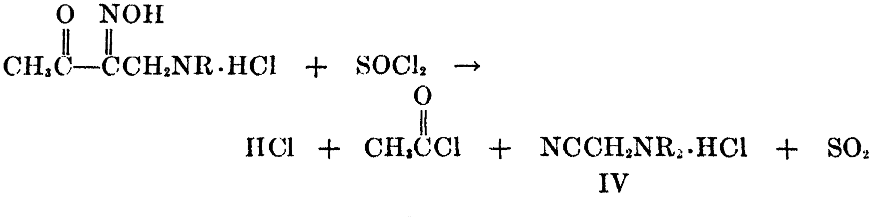
B.



$$\text{II (or free base)} + 3\mathrm{H_2} \longrightarrow \underset{\text{III}}{\mathrm{CH_3\overset{\overset{OH}{|}}{C}H-\overset{\overset{NH_2}{|}}{C}HCH_2NR_2}} + \mathrm{H_2O}$$

The hydrochlorides of the 1-dialkylamino-3-butanones (I) are readily nitrosated by alkyl nitrites in the presence of catalytic quantities of free hydrogen chloride in accordance with reaction A, yielding the corresponding 1-dialkylamino-2-α-oximido-3-butanone hydrochlorides (II). These may be converted to the free bases by treatment with alkali carbonates. A convenient proof of structure of the products is furnished by their reactions with inorganic acid halides (*e.g.*, thionyl chloride or phosphorus oxychloride), which cleave the carbon chain to yield known dialkylaminoethanenitrile hydrochlorides (IV), by reaction C. These products are the result of the well known "second order" Beckmann rearrangement (4) commonly produced in α-oximido ketones by these reagents. It has been established that during this rearrangement the carbon chain

C.



$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}-\overset{\overset{NOH}{\|}}{C}CH_2NR\cdot HCl} + \mathrm{SOCl_2} \rightarrow \mathrm{HCl} + \mathrm{CH_3\overset{\overset{O}{\|}}{C}Cl} + \underset{\text{IV}}{\mathrm{NCCH_2NR_2\cdot HCl}} + \mathrm{SO_2}$$

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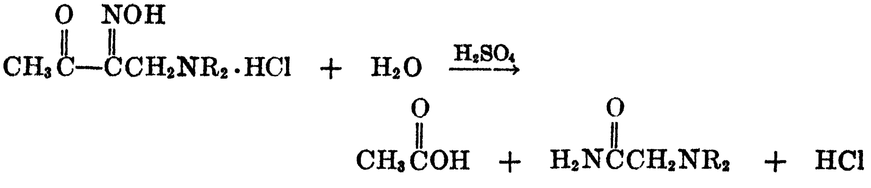
D.



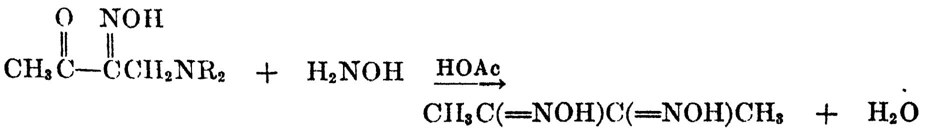
$$CH_3\overset{O}{\overset{\|}{C}}-\overset{NOH}{\overset{\|}{C}}CH_2NR_2\cdot HCl + H_2O \xrightarrow{H_2SO_4} CH_3\overset{O}{\overset{\|}{C}}OH + H_2N\overset{O}{\overset{\|}{C}}CH_2NR_2 + HCl$$

V

of α-oximido ketones is cleaved between the two functional groups; and furthermore, that the α(trans) isomers yield nitriles, whereas the β(cis) isomers yield isonitriles. Thus the formation of dialkylaminoethanenitriles (IV) establishes the structure of compounds II to be 1-dialkylamino-2-α-oximido-3-butanone hydrochlorides, as illustrated. A similar cleavage reaction occurs when II is treated with concentrated sulfuric acid, in this case yielding the corresponding dialkylaminoethanamides (V) instead of the nitriles. Other characteristics of the 1-dialkylamino-2-α-oximido-3-butanones include (a) instability to hot alkali, resulting in the evolution of the dialkylamine substituent as the free dialkylamine, R_2NH, and a slower evolution of hydroxylamine, and (b) the ease with which soluble colored complexes are formed with metallic ions, particularly cupric and ferric ions which yield, respectively, green and yellow solutions. Aqueous solutions of the free bases are yellow, but solutions of their monoacid salts are colorless.

Reaction B, the hydrogenation of 1-dialkylamino-2-α-oximido-3-butanones to 1-dialkylamino-2-amino-3-butanols (III) could not be realized. Both metal-acid reduction (5) and catalytic hydrogenation in the presence of an excess of hydrogen chloride (6), described in the literature as applicable to the formation of amino alcohols or amino ketones from α-oximido ketones, cause extensive hydrogenolysis to form large amounts of both ammonium and dialkylammonium salts. Catalytic hydrogenation of the free bases or their monoacid salts in the absence of free mineral acid, which ordinarily converts α-oximido ketones to substituted pyrazines (7), again results in hydrogenolysis of the dialkylamine substituent to yield the free dialkylamine, R_2NH. Although 1–3 moles of hydrogen are absorbed per mole of II in each of the aforementioned catalytic hydrogenations, no basic material other than ammonia and dialkylamines could be isolated.

The 1-dialkylamino-2-α-oximido-3-butanones are readily converted to the corresponding dialkylaminobutanedione dioximes (VI) by hydroxylamine in buffered acetic acid solution.



$$CH_3\overset{O}{\overset{\|}{C}}-\overset{NOH}{\overset{\|}{C}}CH_2NR_2 + H_2NOH \xrightarrow{HOAc} CH_3C(=NOH)C(=NOH)CH_3 + H_2O$$

VI

The dioximes are similar to the monooximes in their instability to hot alkali and in the ease with which colored complexes are formed with cupric and ferric ions, yielding respectively brown, and yellow solutions. Similarly, solutions of the free bases are yellow whereas those of their monoacid salts are colorless.

All attempts to convert the 1-dialkylamino-2-α-oximido-3-butanones to the corresponding dialkylaminobutanediones failed. The oxidative and hydrolytic methods recorded in the literature (8) for the conversion of α-oximido ketones to α-diketones either resulted in no reaction or caused extensive decomposition. Similar unsuccessful results were obtained in attempts to condense the mono- and di-oximes with urea or *p*-anisidine, and in attempts to obtain substituted furazans by heating the dioximes with ammonium hydroxide (9).

The mono- and di-oximes prepared during this work have been submitted for testing as reagents for the colorimetric determination of iron. The results of these tests will be discussed in a forthcoming paper (10). The compounds were also submitted for evaluation as antimalarial drugs but exhibited no activity.

Acknowledgment. The authors are indebted to Eli Lilly and Company, Indianapolis, Indiana, and to the Purdue Research Foundation for financial assistance in this work.

EXPERIMENTAL

All melting points are corrected.

1-Diethylamino-2-α-oximido-3-butanone (*II*, *R* = C_2H_5). (*A*). *Monohydrochloride.* A solution of 14.3 g. (0.10 mole) of 1-diethylamino-3-butanone (2) in 15 ml. of isopropanol was cooled in an ice-bath and stirred mechanically while anhydrous hydrogen chloride was led in until the solution was barely acid to Congo Red. Two ml. of a saturated solution of anydrous hydrogen chloride in isopropanol was added and then 9.8 g. (0.11 mole) of freshly distilled isopropyl nitrite was introduced dropwise with stirring and cooling at 30–35°. After 30 minutes the mixture was diluted with 50 ml. of ether, stirred an additional 15 minutes, then filtered. The crude hydrochloride thus obtained was 16.3 g., m p. 150–151° (decomp.). Two recrystallizations from a mixture of absolute alcohol and dioxane gave 11.3 g. (54%) of white needles, m.p. 154–155° (decomp.).

Anal. Calc'd for $C_8H_{16}N_2O_2 \cdot HCl$: Cl, 17.02. Found: Cl, 17.21.

(*B*). *Fre eBase.* The crude hydrochloride (16.3 g.) was stirred into a solution of 21.5 g. (100% molar excess) of potassium carbonate in 43 ml. of water. The precipitated free base was extracted with ether, which was separated and carefully evaporated. The residue was allowed to crystallize, then dried under vacuum. Recrystallization from 250 ml. of ligroin (b.p. 35–37°) with decolorization and final cooling to 0° gave 11.4 g. (73%, based on 1-diethylamino-3-butanone) of 1-diethylamino-2-α-oximido-3-butanone, white needles, m.p. 53–55°.

Anal. Calc'd for $C_8H_{16}N_2O_2$: N, 16.27. Found: N, 16.26, 16 28.

(*C*). *Structure proof.* Five g. of pure 1-diethylamino-2-α-oximido-3-butanone hydrochloride was mixed with 20 ml. of thionyl chloride and stirred until the evolution of gases was complete. The solution was then evaporated to dryness under vacuum, and the residue dissolved in 20 ml. of methanol, decolorized, filtered, and reprecipitated with 100 ml. of dioxane. The precipitate was recrystallized twice from a mixture of methanol and dioxane, yielding 2.0 g. (56%) of diethylaminoethanenitrile hydrochloride (IV, R = C_2H_5), white needles, m.p. 191–192° (decomp.). [Lit. (11) m.p. 192°.]

Anal. Calc'd for $C_6H_{12}N_2 \cdot HCl$: N, 18.84; Cl, 23.89.
Found: N, 18.96; Cl, 24.14.

Five g. of pure 1-diethylamino-2-α-oximido-3-butanone hydrochloride was dissolved in 10 ml. of concentrated sulfuric acid. The solution was allowed to stand one hour, then poured onto 100 g. of chipped ice and immediately made basic with 70 g. of ice-cold 50%

sodium hydroxide solution. The product was extracted with ether, which was carefully evaporated. The residual oil crystallized on cooling. It was dried under vacuum, then recrystallized from 50 ml. of ligroin (b.p. 90–100°) with final cooling to 0°, yielding 1.9 g. (62%) of diethylaminoethanamide (VI), white needles, m.p. 76–77° [Lit. (11) m.p. 77°].

Anal. Calc'd for $C_6H_{14}N_2O$: N, 21.52. Found: N, 21.70.

1-(N-Piperidino)-2-α-oximido-3-butanone (II, R_2 = C_5H_{10}). (A). Monohydrochloride. A solution of 19.2 g. (0.10 mole) of 1-(N-piperidino)-3-butanone hydrochloride (3) and 1 ml. of a saturated solution of hydrogen chloride in isopropanol was stirred and cooled to 30–35° while 9.8 g. (0.11 mole) of freshly distilled isopropyl nitrite was added dropwise. After 15 minutes the mixture was diluted with 200 ml. of ether, and allowed to stand an additional 10–15 minutes. The precipitated crude hydrochloride weighed 21.8 g. and melted at 218–219° (decomp.). Two recrystallizations from 95% alcohol gave 15.2 g. (69%) of white platelets, m.p. 228–229° (decomp.).

Anal. Calc'd for $C_9H_{16}N_2O_2 \cdot HCl$: Cl, 16.09. Found: Cl, 16.11, 16.24.

(B). Free base. A solution of 21.8 g. of the crude hydrochloride in 65 ml. of water was poured into a solution of 27.6 g. (100% molar excess) of potassium carbonate in 28 ml. of water. The mixture was stirred 15 minutes, the precipitated solid was filtered off, rinsed with saturated sodium chloride solution, and dried at 60°. The product was extracted with 1 liter of boiling ligroin (b.p. 90–100°), decolorized with charcoal, filtered, and allowed to crystallize at 0°. Yield, 11.2 g. [61%, based on 1-(N-piperidino)-3-butanone hydrochloride] of white plates, m.p. 132–133°.

Anal. Calc'd for $C_9H_{16}N_2O_2$: C, 58.69; H, 8.74; N, 15.20.

Found: C, 58.67, 58.65; H, 8.69, 8.79; N, 15.24, 15.13.

(C). Structure proof. Five g. of pure 1-(N-piperidino)-2-α-oximido-3-butanone hydrochloride was dissolved in 10 ml. of concentrated sulfuric acid. The solution was warmed at 90–95° for one hour, cooled to room temperature, and poured onto 100 g. of chipped ice. The product was precipitated with 70 g of ice-cold 50% sodium hydroxide solution, and extracted with ether. Evaporation of the ether and recrystallization of the residue from ligroin (b.p. 90–100°) gave 2.1 g. (65%) of 2-(N-piperidino)ethanamide (VI), white platelets, m.p. 111° [Lit. (12) m.p. 108]°.

Anal. Calc'd for $C_7H_{14}N_2O$: C, 59.14; H, 9.92; N, 19.69.

Found: C, 59.13, 59.07; H, 9.92, 9.85; N, 19.64, 19.73.

Dialkylaminobutanedione dioximes (VI). General procedure. A mixture of 0.10 mole of the appropriate 1-dialkylamino-2-α-oximido-3-butanone hydrochloride, 14.0 g. (0.20 mole) of hydroxylamine hydrochloride, 30.4 g. (0.31 mole) of potassium acetate, 80 ml. of water, and 6.0 g. (0.10 mole) of acetic acid was stirred and heated at 90–95° for one hour, cooled to room temperature, and neutralized to litmus with 50% potassium hydroxide solution. A solution of 27.6 g. (0.20 mole) of potassium carbonate in 28 ml. of water was added and the precipitated oil was stirred until it solidified. It was then filtered off, ground to a paste with water, filtered again, rinsed well with water, and dried at 60°. The product was the crude dioxime.

Diethylaminobutanedione dioxime (VI, R = C_2H_5*). (A). Free Base.* The general procedure gave 17.8 g. of crude dioxime, m.p. 110–112°, from 20.9 g. of 1-diethylamino-2-α-oximido-3-butanone hydrochloride. It was dissolved in 250 ml. of boiling carbon tetrachloride, stirred with charcoal, filtered, and reprecipitated by cooling to 0°. Yield, 16.5 g. (88%) of white plates, m.p. 110–112°.

Anal. Calc'd for $C_8H_{17}N_3O_2$: C, 51.31; H, 9.14; N, 22.45.

Found: C, 51.36, 51.29; H, 9.19, 9.13; N, 22.44, 22.38.

(B). Monohydrochloride. The pure free base was dissolved in twice its weight of absolute alcohol. Anhydrous hydrogen chloride was passed into the solution until it was acid to Congo Red and the product was precipitated by slowly adding 10 volumes of dry ether. The crystals were dried at 60°; yield, 93–94% of compact white crystals, m.p. 176–178° (decomp.).

Anal. Calc'd for $C_8H_{17}N_3O_2 \cdot HCl$: Cl, 15.88. Found, Cl, 15.81, 15.92.

1-(N-Piperidino)butanedione dioxime (VI, R_2 = C_5H_{10}). (A). Free base. The general procedure yielded 18.3 g. of crude dioxime, m.p. 161–162° (decomp.), from 22.1 g. of 1-(N-piperidino)-2-α-oximido-3-butanone hydrochloride. It was dissolved in 400 ml. of boiling toluene, decolorized, and filtered through a preheated funnel. Cooling the filtrate precipitated 17.3 g. (87%) of white plates, m.p. 166–167° (decomp.).

Anal. Calc'd for $C_9H_{17}N_3O_2$: C, 54.27; H, 8.58; N, 21.09.

Found: C, 54.44, 54.31; H, 8.60, 8.68; N, 21.10, 20.96.

(B). Monohydrochloride. The pure free base was dissolved in three times its weight of hot absolute alcohol. Anhydrous hydrogen chloride was passed into the solution until it was acidic to Congo Red. It was then diluted with 5 volumes of dry ether and allowed to stand one hour. The solid product was dried at 60°; yield, 98–100% of compact white crystals, m.p. 206–207° (decomp.).

Anal. Calc'd for $C_9H_{17}N_3O_2\cdot HCl$: Cl, 15.06. Found: Cl, 15.08, 15.15.

SUMMARY

The synthesis, configurational identification, and reactions of the mono- and di-oximes of two dialkylaminobutanediones are described.

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[Contribution from the Eastern Regional Research Laboratory[1]]

PREPARATION AND POLYMERIZATION OF ACRYLIC ESTERS OF OLEFINIC ALCOHOLS

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Received August 13, 1946

In connection with projects (1) concerned with the production and subsequent cross-linkage of unsaturated acrylic resins, various monomers containing two or more olefinic linkages were required. This paper describes the preparation of several alkenyl acrylates that seemed suitable for the preparation of soluble unsaturated acrylic copolymers because of the presence of the highly polymerizable acrylate double bond and the relatively unreactive olefinic linkages of the alkoxyl groups. There is little published information on alkenyl acrylates (2, 3), but several alkenyl methacrylates, including the allyl (3),methallyl (3, 4), oleyl (4), furfuryl (5), *alpha*-triphenylmethallyl (6), and vinyl (7, 8, 9) esters, have been prepared.

The alcoholysis method was found useful in the present work for making alkenyl acrylates, but the yields (Table I) were generally lower than those obtained in the preparation of alkyl acrylates (10).

The allyl (3), methallyl (3), and the *beta*-chloroallyl acrylates were prepared also by pyrolysis of the corresponding *alpha*-acetoxypropionates, but the yields were low. Negligible yields of crotyl and methyl vinyl carbinyl acrylates were obtained in the pyrolysis of the corresponding acetoxypropionates, but butadiene was formed in high yields from both esters.

The relative tendencies of the alkenyl acrylates to form insoluble (presumably cross-linked) copolymers with methyl acrylate were estimated by polymerizing various percentages of the ester with methyl acrylate in ethyl acetate and comparing the minimum concentration of alkenyl acrylate required to produce gelation of the copolymer solution. The most active monomers were the methallyl and *beta*-chloroallyl acrylates, whereas crotyl acrylate had the least tendency to cause gelation (Table II). Although 0.1% of methallyl acrylate produced gelation, approximately forty times as much of the isomeric crotyl acrylate was required. Whether the alkenyl acrylates would have the same relative gelling effects when polymerized with monomers other than methyl acrylate was not determined.

Several of the ethyl acetate solutions containing soluble copolymers (Table II) were used to prepare cross-linked films. Benzoyl peroxide (2 to 5% of the copolymer) was dissolved in the solution. The viscous solution was applied to a flat surface, and the solvent was allowed to evaporate. The resulting films as such could be readily redissolved in organic solvents. After being heated at about 80° for a short time, however, the films were insoluble. It was observed that similar treatment of polymerized alkyl acrylates, that is, acrylic resins containing no olefinic unsaturation, also yielded insoluble films.

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[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

TABLE I
OLEFINIC ESTERS OF ACRYLIC ACID

ESTER	YIELD %[a]	CONVERSION, %[b]	METHYL ACRYLATE LOST, %	B.P. °C.	PRESS., MM	n_D^{20}	d_4^{20}	MOL. REFRACTION		SAP. EQUIV.	
								Calc'd[c]	Found	Calc'd	Found
Allyl	70	70	—	47	40	1.4320	0.9441	30.63	30.80	112.1	112.4
beta-Methallyl	74	56	2	68	50	1.4372	.9285	35.25	35.60	126.1	128.3
Methyl vinyl carbinyl[d]	37	27	1	70	97	1.4299	.9066	35.25	35.94	126.2	128.2
Crotyl	69	59	10	60	23	1.4422	.9344	35.25	35.73	126.2	128.5
beta-Chloroallyl	56	33	—	72	29	1.4600	1.1243	35.50	35.70	146.6	140.5
gamma-Chloroallyl	68	34	27	87	34	1.4680	1.1385	35.50	35.79	146.6	146.0
4-Methyl-4-penten-2-yl	70	40	9	62	14	1.4380	0.9027	44.48	44.85	154.2	151.2
Citronellyl[d]	91	90	27	108	5.4	1.4500	.8879	62.95	63.66	210.3	216.6
Geranyl	64	59	13	116	6.2	1.4690	.9121	62.49	63.60	208.3	212.4
Rhodinyl[d]	80	79	18	107	4.2	1.4591	.9026	62.95	63.71	210.3	214.4
Cinnamyl	71	52	13	108	1.2	1.5508[e]	1.0495[e]	54.74	57.20	188.2	191.8
Furfuryl	86	86	17	93	16	1.4800	1.1125	38.84	38.85	152.1	150.9

[a] On basis of unrecovered alcohol.

[b] On basis of total alcohol used.

[c] No correction was made for the exaltation owing to conjugated double bonds.

[d] The purity of this sample is questionable, since separation of the alcohol from the ester was difficult.

[e] At 25°.

TABLE II
GELATION OF COPOLYMERS OF METHYL ACRYLATE

EXPT. NO.	POLYFUNCTIONAL MONOMER	CONCENTRATION, % OF TOTAL MONOMER	
		No gel formed	Gel formed
1	*beta*-Methallyl acrylate	0.05	0.10
2	*beta*-Chloroallyl acrylate	.05	.10
3	Allyl acrylate	.10	.20
4	*beta*-Methallyl methacrylate	.10	.20
5	Cinnamyl acrylate	.10	.20
6	4-Me.-4-penten-2-yl acrylate	.10	.20
7	*alpha*-Carballyloxyethyl acrylate[a]	.10	.20
8	*gamma*-Chloroallyl acrylate	.10	.20
9	Allyl methacrylate	.20	.30
10	Geranyl acrylate	.30	.50
11	CR-39 monomer[b]	.50	.80
12	Furfuryl acrylate	1.00	2.00
13	Rhodinyl acrylate	2.00	3.00
14	Citronellyl acrylate	2.00	3.00
15	Bis-(allyl lactate) maleate[c]	2.00	5.00
16	Crotyl acrylate	3.00	4.00

[a] Preparation and physical properties described in another paper, Rehberg, Dixon, and Fisher, *J. Am. Chem. Soc.*, **67**, 208 (1945).

[b] Additional data on this allyl monomer [$O(CH_2CH_2OCOOCH_2CH:CH_2)_2$] have been given by Coles, Deuberry, and Curry, *J. Optical Soc. Am.*, **34**, (10), 623 (Oct. 1944) and by Pechukas, Strain, and Dial, *Modern Plastics*, **20**, 101 (1943).

[c] Prepared in a separate investigation; will be described in a later publication.

EXPERIMENTAL

Preparation of monomeric esters. The acrylic esters (Table I) were prepared by the alcoholysis of methyl acrylate, using essentially the procedure described previously (10). One important variation from that procedure was the use of alkaline catalysts and polymerization inhibitors in experiments in which there appeared to be danger that mineral acid would cause polymerization, isomerization, or decomposition of the olefinic alcohol or its ester. Aluminum alcoholate was the preferred catalyst and phenyl-*beta*-naphthylamine was used as polymerization inhibitor when the alcoholate was used as catalyst. Commercially available aluminum isopropoxide was satisfactory, though in a few experiments amalgamated aluminum foil was dissolved in the olefinic alcohol at the beginning of the experiment. Allyl and *beta*-chloroallyl acrylates were prepared with sulfuric acid as catalyst, but in all the other experiments aluminum alcoholate was used.

TABLE III

Physical Constants of Olefinic Alcohols

ALCOHOL	BOILING POINT, °C. (MM.)		REFRACTIVE INDEX, n_D^{20}		SOURCE
	Observed	Literature	Observed	Literature	
Allyl	97	96.9[a]	1.4134	1.4135[a]	Shell Chemical Corp.
Methallyl	114	114.5[a]	1.4255	1.4255[a]	" " "
beta-Chloroallyl	133–134	134[a]	—	1.460[a]	" " "
gamma-Chloroallyl	147–149	147–153[a]	1.4655	—	" " "
Crotyl	122–123	123[a]	1.4300	1.430[a]	" " "
Me. vinyl carbinyl	97	97[a]	—	1.415[a]	" " "
4-Me.-4-penten-2-yl	40/13	—	1.4330	—	" " "
Geranyl	132/27	129/25[b]	1.4760	1.4766[e]	Eastman Kodak Co., (Tech. grade)
Citronellyl	105/10	106–108/12[d]	1 4522	1.4566[b]	Eastman Kodak Co. (White Label)
Rhodinyl	114/15 113–114/15	118–119.5/18[c] 113–114/15[c]	1.4625	1.4588 (15°)[c]	Eastman Kodak Co. (Technical)
Cinnamyl	110–112/4	143–145/14[b]	1.5835 (25°)	1.5819[b]	Eastman Kodak Co. (Practical)
Furfuryl	—	83–84/25[f]	1.4874	1.4868[f]	Eastman Kodak Co., (White label)

[a] Technical data supplied by Shell Chemical Corp.

[b] Heilbron and Bunbury, "Dictionary of Organic Compounds," **1943**, Oxford University Press, New York.

[c] Simonsen, The Terpenes, Vol. I, **1931**, The University Press, London.

[d] Karrer, Geiger, Rentschler, Zbinden, and Kugler, *Helv. Chim. Acta*, **26**, 1741 (1943).

[e] Handbook of Chemistry & Physics, 27th Ed., 2553 pp. (1943), Chemical Rubber Publishing Co., Cleveland, Ohio.

[f] Dunlop and Trimble, *Ind. Eng. Chem* , **32**, 1000 (1940).

No attempt was made to determine whether double bonds migrated during the alcoholysis, but Day (11) prepared alkenyl esters by alcoholysis in the presence of aluminum alcoholate, hydrolyzed the resulting esters, examined the olefinic alcohols, and found that little or no migration had occurred. Redistilled samples of alcohols were used in the alcoholysis experiments. The sources of the alcohols and physical constants of the redistilled samples are given in Table III.

Allyl(3), methallyl(3), and *beta*-chloroallyl acrylates and allyl and methallyl methacrylates were prepared by pyrolysis of the corresponding *alpha*-acetoxypropionates and *alpha*-acetoxyisobutyrates, respectively. We have greatly improved the yield of allyl and methallyl lactates and simplified the procedure for their preparation. The following procedure has consistently produced 90% conversion to the allyl ester in a single treatment of lactic acid with allyl alcohol.

Direct esterification of lactic acid. Ten moles (1125 g.) of 80% edible lactic acid, 400 cc. of benzene, and 5 cc. of sulfuric acid were refluxed in a still having a 3-foot column fitted with a water trap at its top, water being drawn off as it collected (300 cc. in 5 hr.). When production of water became slow, 40 moles (2323 g.) of allyl alcohol was added and refluxing continued, with removal of water (220 cc., containing some allyl alcohol, in 20 hr.). When no more water was produced, the flask was cooled, 20 g. of anhydrous sodium acetate was added to neutralize the sulfuric acid, and the benzene was distilled at atmospheric pressure as its azeotrope with allyl alcohol. The remainder of the alcohol was then distilled fairly rapidly under about 50 mm. pressure, after which the allyl lactate was rapidly distilled at 60° (7 mm.). The yield was 1178 g., or 90.5%.

TABLE IV

MONO- AND DI-ESTERS OF LACTIC ACID

ESTER	YIELD, %	B.P., °C.	PRESS., MM.	n_D^{30}	d_4^{30}	MOL. REFRACTION		SAP. EQUIV.	
						Calc'd	Found	Calc'd	Found
ALKENYL LACTATES									
beta-Chloroallyl	76	83	5	1.4627	1.2153	37.49	37.28	164.6	163.2
gamma-Chloroallyl	65	106	12	1.4670	1.2166	37.49	37.54	164.6	161.9
Crotyl[a]	83	92	18	1.4420	1.0106	37.24	37.75	144.2	149.3
Methyl vinyl carbinyl	77	58	8	1.4326	1.0091	37.24	37.10	144.2	144.5
ALKENYL *alpha*-ACETOXYPROPIONATES									
beta-Chloroallyl	84	96	5	1.4460	1.1792	46.85	46.73	103.3	102.0
Crotyl[a]	86	94	8	1.4347	1.0338	46.60	46.97	93.1	95.1
Methyl vinyl carbinyl	100	80	8	1.4256	1.0233	46.60	46.59	93.1	93.2

[a] This ester was not pure; the nature of the impurities is not known.

With the procedure described above, *beta*-chloroallyl lactate was prepared in 76% yield. Methyl vinyl carbinol and crotyl alcohol appeared to be somewhat unstable in the presence of sulfuric acid, so for the preparation of their lactates the foregoing procedure was modified somewhat. The lactic acid, alcohol, and benzene were mixed and refluxed with removal of water until little water was produced. Then 10 g. of *p*-toluenesulfonic acid was added, and heating continued. When no more water was produced, the catalyst was neutralized and the product distilled as described above.

Alcoholysis of lactic esters. Methallyl and *gamma*-chloroallyl lactates were prepared by alcoholysis of methyl or ethyl lactate. Three moles (312 g.) of methyl lactate, 6 moles (555 g.) of *gamma*-chloroallyl alcohol, and 10 g. of aluminum *tert.*-butoxide were mixed and refluxed in a still, from which methanol was withdrawn as fast at it collected at the still-head. When production of methanol ceased, the excess alcohol was distilled at 54° (13 mm.), after which the product was obtained at 105° (12 mm.); yield, 65%. This procedure, using methallyl alcohol, gave a 70% yield of methallyl lactate.

Acetylation of alkenyl lactates. All the alkenyl alpha-acetoxypropionates (Table IV) were prepared by using a slight excess of acetic anhydride with the appropriate lactate.

Pyrolysis of alkenyl alpha-acetoxypropionates. The apparatus and procedure previously described(3) for the pyrolysis of allyl and methallyl *alpha*-acetoxypropionates and *alpha*-acetoxyisobutyrates were used in the pyrolysis of *beta*-chloroallyl, crotyl, and methyl vinyl carbinyl *alpha*-acetoxypropionates. As was expected, the principal products obtained by the pyrolysis of the two latter esters were butadiene, acetic acid, acetaldehyde, and carbon monoxide, little of the corresponding acrylic esters being produced. β-Chloroallyl *alpha*-acetoxypropionate gave a fair yield of the acrylate; other products were not identified (Table V).

Because of the discouraging results from the other esters, *gamma*-chloroallyl lactate was not acetylated and pyrolyzed.

Determination of gelation tendency. In each experiment, 20 g. of methyl acrylate and 0.05 g. of benzoyl peroxide were dissolved in 80 g. of ethyl acetate, and the desired percentage of the polyfunctional monomer, based on the total mixture of monomers, was added. The flask containing the mixture was then fitted with an upright condenser and placed in a bath, which was kept at 60° for 24 hours and then at 80° for another 24 hours. The contents of the flasks were then examined for evidence of gelation. The products ranged from sirupy solutions to firm, elastic, solid gels. When the solutions could be poured from the flasks, even though they were sometimes ropy or stringy, they were recorded as not gelled.

TABLE V

PYROLYSIS OF ALKENYL *alpha*-ACETOXYPROPIONATES

ESTER	TEMP., °C.	CONTACT TIME, SEC.[a]	% CRACKED	ACRYLATE	
				Yield, %[b]	Conversion, %[c]
beta-Chloroallyl	525	9.7	68	43	29
Crotyl	500	8.5	85	5	4
Methyl vinyl carbinyl	525	9.1	87	7	6

[a] Based on free space in the heated zone of the Pyrex-glass pyrolysis tube.
[b] On basis of unrecovered ester.
[c] On basis of total ester used.

The lowest tested concentrations of cross-linking comonomers which produced gelation and the highest tested concentrations which failed to produce gelation are shown in Table II. On the basis of earlier work(12, 13), it seems likely that results different from those of Table II would have been obtained in solutions of higher or lower concentration and at different temperatures and catalyst concentrations. The present tests were made under uniform conditions, however, and the results of Table II should represent the relative tendencies of the monomers to form cross-linked polymers.

Mass polymerization. The monomers were placed in elongated Pyrex-glass test tubes (approximately 6 mm. I.D. and 200 mm. long), and the end of the tube was sealed. Small quantities of benzoyl peroxide were included in some experiments. The resulting ampoules were allowed to stand at room temperature until polymerization occurred. The polymers were transparent, infusible, and insoluble. All were hard and strong except the citronellyl, rhodinyl, geranyl, and cinnamyl polymers, which were elastic and gel-like and had little strength.

SUMMARY

The acrylic esters of allyl, methallyl, methyl vinyl carbinyl, crotyl, *beta*-chloroallyl, *gamma*-chloroallyl, methylpentenyl, citronellyl, geranyl, rhodinyl, cinnamyl, and furfuryl alcohols were prepared by alcoholysis of methyl acrylate.

Polymerization of these alkenyl acrylates yielded insoluble, cross-linked resins. When copolymerized with methyl acrylate, methallyl and *beta*-chloroallyl acrylates had the greatest tendency to form cross-linked polymers and crotyl acrylate had the least.

The preparation and pyrolysis of *beta*-chloroallyl, crotyl, and methyl vinyl carbinyl acetoxypropionates are described.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

REACTIONS AND ANALYSIS OF β-CHLOROETHYL SULFIDE IN WATER[1]

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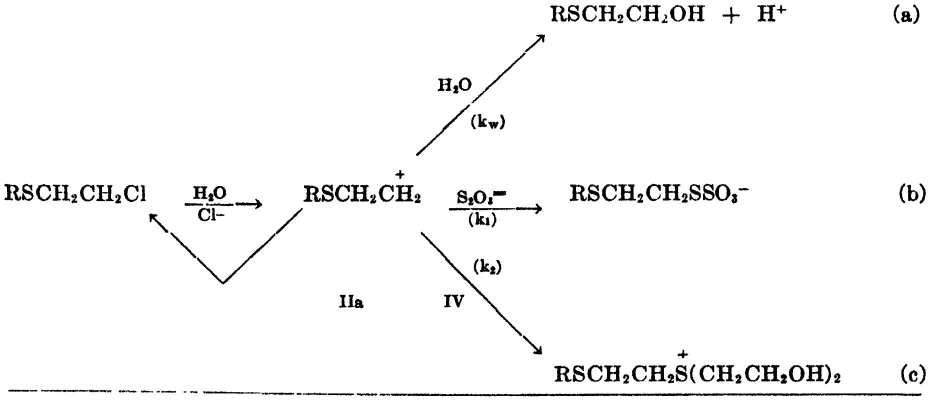
The observations of Peters and Walker (1) and Mohler and Hartnagel (2) that the rate of hydrolysis of β-chloroethyl sulfide (I) in water was first order, independent of the *p*H and a number of added anions and cations, led the latter authors to point out that this behavior resembled that of an S_{N1} process proceeding by a solvolytic mechanism in which the rate controlling step was an ionization of the carbon-chlorine bond.

$$\begin{tikzcd}
\underset{\text{I}}{ClCH_2CH_2SCH_2CH_2Cl} \arrow[r, "H_2O"] & \underset{\text{IIa}}{ClCH_2CH_2SCH_2\overset{+}{C}H_2} \quad Cl^- \arrow[d, "H_2O"] \\
\underset{\text{IV}}{(HOCH_2CH_2)_2S} & \underset{\text{III}}{ClCH_2CH_2SCH_2CH_2OH} + H^+ \arrow[l, "H_2O"']
\end{tikzcd}$$

The solvolytic nature of the reaction is substantiated by the observations (1, 2) that alcohol as a solvent markedly decreases the rate, propanol being more effective than ethanol which in turn is more effective than methanol (2), as expected for a solvolytic reaction.

In unpublished work, Peters and Ogston have made the significant discovery that, in the presence of a number of compounds, especially thiol and sulfide derivatives, the rate of the reaction remains essentially unchanged, although the course of the reaction becomes metathesis rather than hydrolysis. These observations were interpreted on the basis of the ionic intermediate IIa above.



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[1] The work described in this paper was carried out under a contract, recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the University of Illinois.

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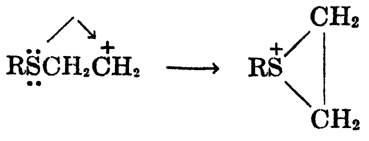
Since the common behavior of reactions proceeding through a cation of the type IIa is that the ion reacts immediately with the solvent, regardless of other reagents present, it seems necessary to postulate some other type of intermediate. The most likely form would be a cyclic sulfonium salt (IIb).



IIa IIb

Such an intermediate, although considerably more reactive than I, would be stable enough to discriminate between the molecular species with which it might react. A very much higher value for k_1 than for k_w would therefore change the course of reaction from hydrolysis (a) to metathesis (b, c) in the presence of even relatively small concentrations of thiosulfate. The ratio of these rate constants has been termed the "competition factor" by Peters and Ogston, who found the competition factor for thiosulfate (k_1/k_w) to be 2.7×10^4.

This has suggested that a convenient procedure for analysis of β-chloroethyl sulfide in the presence of hydrolysis products might be devised making use of its "thiosulfate-demand". Since both hydrolysis and metathesis involved the same rate-controlling step the rates of both processes would be the same. In water at 25°, the value for this constant is about 0.10 min.$^{-1}$ (1, 2), which corresponds to a half-life of about seven or eight minutes. Either reaction would thus be about 96% complete in forty minutes. These expectations have been verified experimentally and the method utilized to confirm the rate of hydrolysis of I in water.

In addition, some observations are recorded on the stability of vapor of I in moist air. As would be expected from the mechanism of hydrolysis outlined above, hydrolysis in the "nonpolar solvent" air did not proceed measurably over a two-week period. Exposure of the vapor of I to liquid water (or synthetic seawater) did lead to absorption and hydrolysis, to some extent favored by an oil film on the water.

EXPERIMENTAL

Analysis of aqueous β-chloroethyl sulfide solutions. Approximately 1% solutions of pure redistilled β-chloroethyl sulfide (prepared by the action of thionyl chloride on thiodiglycol) were made up by dissolving weighed quantities in 100 cc. of anhydrous Cellosolve, Methyl Cellosolve, or dioxane. One-cc. portions of these solutions were pipetted into 25-cc. portions of 0.01 *N* sodium thiosulfate, and, after periods of 5, 10, 15, 25, 40, and 80 minutes at room temperature (*ca.* 27°), a 25-cc. portion of 0.01 *N* iodine in potassium iodide was added to each mixture. The excess of iodine was then back-titrated with thiosulfate. The results of the measurements of the rate are summarized in Table I. The first order rate constants included were estimated graphically. For the first three experiments, the I was added in dioxane solution, for the fourth, in Methyl Cellosolve, and for the last two, in Cellosolve.

Since the reactions were essentially complete after forty minutes, this time was chosen in carrying out analysis for I by this procedure. The average of the forty-minute values from Table I, 95.97% with a mean deviation of 2.4%, compares favorably with the theoretical value of 96.9% calculated on the basis of a half-life for the reaction of eight minutes. Some hydrolysis (rather than metathesis) may take place in dilute thiosulfate solution but, in 0.01 *N* thiosulfate, it should amount to less than 1% of the over-all reaction, based on Peters and Ogstons' value of 2.7 × 10^4 for the "competition factor" of thiosulfate ion.

As a further check on the analytical procedure, the rate of hydrolysis of I in aqueous solution was measured and found to be the same as the rate of reaction with thiosulfate ion. One-cc. portions of solutions of I were added to 25-cc. portions of distilled water at room temperature (*ca.* 27°). After periods of 5, 10, 15, 25, 40, and 80 minutes, 25 cc. of 0.01 *N* thiosulfate was added to each mixture and, forty minutes later, the unreacted thiosufate was titrated with 0.01 *N* iodine solution. On the basis of 96% reaction with thiosulfate after forty minutes, the total amount of I in the solution at the time of addition of thiosulfate was readily estimated. The data for the rate of hydrolysis as measured in this manner are summarized in Table II.

TABLE I

RATE OF REACTION OF β-CHLOROETHYL SULFIDE WITH AQUEOUS SODIUM THIOSULFATE (*CA.* 27°)

TIME (MIN.)	% HYDROLYSIS						AVERAGE
	(Dioxane)			(Methyl Cellosolve)	(Cellosolve)		
5	41.1	45.7	38.5	44.1	48.2	34.5	
10	63.8	66.2	63.7	66.1	72.8	55.3	
15	78.0	79.3	79.6	82.4	87.2	66.1	
25	90.8	93.0	89.5	93.2	96.4	84.2	
40	96.3	96.0	93.5	97.8	100.5	91.0	95.9 ± 2.4
80	97.3	97.3	94.9	99.4	—	92.4	
Rate Constant (min.$^{-1}$)	0.098	0.097	0.101	0.097	0.127	0.083	0.101 ± .009

TABLE II

RATE OF HYDROLYSIS OF β-CHLOROETHYL SULFIDE IN WATER (*CA.* 27°)

	% HYDROLYSIS	
5	40.4	41.3
10	65.9	69.3
15	80.8	83.8
25	92.5	97.5
40	95.7	100.
80	97.3	
Rate Constant (min.$^{-1}$)	0.108	0.118

Stability of β-chloroethyl sulfide vapor in moist air. A one-liter flask, fitted with a 24/40 standard-taper ground joint, was equipped with an inner joint carrying a short glass tube and a stopcock. This flask was evacuated to a pressure of 4 to 5 mm. Moisture was removed either by heating with a free flame during evacuation or by alternately refilling with air dried by passage through calcium chloride and reevacuating several times. Finally the evacuated, dried flask was connected to a Geissler potash-bulb apparatus, the three bulbs of which were filled with I, and slowly allowed to refill by passage of dry air through the bubbler (15 to 20 minutes). In this way a definite volume of air, essentially saturated with mustard vapor, was obtained. If the presence of moisture was desired, one cc. of water was added to the flask before evacuating, and the process of evacuation continued until the last of the liquid water evaporated. This gave a saturated vapor at the pressure finally prevailing in the flask, amounting to about 40 to 50 mg. of water per liter of vapor.

To effect the absorption of the vapors, a small volume of Cellosolve,[3] usually 5 cc., was added to the flask and spread out over the walls by rotating the flask periodically. A period of one hour was allowed for absorption: the liquid contents of the flask were then washed out into a measured amount of standard thiosulfate and after forty minutes, the excess thiosulfate was titrated with iodine. For the very small amounts of I encountered (about 0.5 mg.) 0.001 *N* solutions were used. These dilute solutions were made up and standardized frequently.

TABLE III

DETERMINATION OF β-CHLOROETHYL SULFIDE VAPOR PRESENT IN A LITER OF SATURATED DRY AIR

GLASS FLASK		COPPER FLASK	
Absorbed at once	Absorbed after 15 hours	Absorbed at once	Absorbed after 15 hours
0.68 mg.	0.52 mg.	0.72 mg.	0.54 mg.
.73	.51	.59	.55
	.56		.75
	0.63 ± .10		.73
			0.65 ± .08

TABLE IV

DETERMINATION OF β-CHLOROETHYL SULFIDE VAPOR PRESENT IN A LITER OF SATURATED MOIST AIR

GLASS FLASK		COPPER FLASK	
Absorbed at once	Absorbed after 15 hours	Absorbed at once	Absorbed after 15 hours
0.65 mg.	0.47 mg.	0.51 mg.	0.60 mg.
.59	.68	.48	.50
.61	.51	.55	.59
.63		.52	.56
	0.55 ± .08	.72	
0.62 ± .02		.67	0.56 ± .03
		.67	
	after 142 hrs.	.53	after 120 hrs.
	0.57 mg.	.58 ± .08	0.52 mg.

A summary of the results is given below in Tables III and IV. Each value is the result of a separate determination. Although there is a faint indication of hydrolysis of the moist vapor, the deviations in this direction are probably within the limits of experimental error.

The value of 0.64±.09 mg. of I per 1025 cc. of air saturated by bubbling through the liquid checks well with measurements by Yablick, Perrott, and Furman (3), who found 0.0062–

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[3] When dioxane was used, the results were erratic, apparently due to the tendency for peroxide formation in the dioxane.

.0004 mg. of I per 11 cc. of vapor similarly prepared. This is about half the concentration to be expected for saturated vapor on the basis of the vapor pressure as measured by Mumford, Phillips, and Ball (4). However, these authors mentioned that most of the previous estimates of the vapor pressure of I at 20° were just about half the value they found.

TABLE V

DETERMINATION OF β-CHLOROETHYL SULFIDE IN A LITER OF VAPOR

ABSORBED BY 6 CC. OF CELLOSOLVE	ABSORBED BY 6 CC. OF CELLOSOLVE & 1 CC. OF H_2O
0.65 mg.	0.53 mg.
.51	.57
.76	.68
.63	.58
.53	.54
.60	.54
.68	.52
.54	.50
	.55
0.61 ± .07 mg.	.56
	.62
	0.56 ± .04 mg.

TABLE VI

AMOUNT OF β-CHLOROETHYL SULFIDE REMAINING AFTER EXPOSURE OF 1 LITER OF VAPOR TO 1 CC. OF LIQUID WATER

DISTILLED WATER				"SEA" WATER			
½ hr.	2 hrs.	15 hrs.	½ hr. (with oil)	½ hr.	2 hrs.	15 hrs.	½ hr. (with oil)
0.28 mg.	0.06 mg.	0.03 mg.	0.13 mg.	0.41 mg.	0.28 mg.	0.05 mg.	0.41 mg.
.26	.09	.00	.17	.45	.08	.07	.54
.23	.09	.00	.22	.44	.08	.05	.37
.31	.06	.01	.16	.53	.28	.01	.50
.32	.10		.24		.14	.02	.54
.27		0.01 ± .01	.14	0.46 ± .03		.05	.41
	0.08 ± .02		.21		0.17 ± .08	.00	.47
0.27 ± .02			.14			.02	
			.14			.09	0.45 ± .05
						.00	
			0.17 ± .03				
						0.03 ± .03	

Reaction of β-chloroethyl sulfide vapor with liquid water. The reactions of mustard vapor with water were carried on in the same apparatus described above. Since experiments with one cc. of liquid water in the flask would give absorbent contaminated with water, the effect of water in the Cellosolve used as absorbent has been investigated. It has been found that absorption of mustard vapor in 6 cc. of Cellosolve and one cc. of water gives values about 10% lower than without water. The results are summarized in Table V.

To measure the rate of hydrolysis of mustard vapor in the presence of liquid water, 1.0 cc. of water was added through the stopcock to the flask containing the saturated vapor.

The flask was then rotated periodically to spread the water over the walls of the flask in order to offer a large surface for absorption of the I. At the end of a specified interval, half an hour, two hours or fifteen hours, 6 cc. of Cellosolve was added. Absorption and analysis for unreacted I were carried out as described above. The results are summarized in Table VI. The values have been corrected for the 10% hydrolysis which may occur during absorption.

Some of the reactions were carried out with distilled water, some with a synthetic "sea" water, prepared by dissolving 28 g. of sodium chloride, 8.5 g. of magnesium chloride hexahydrate, 2 g. of potassium sulfate, and 2 g. of calcium chloride in one liter of distilled water.

To ascertain whether a film of oil on the water might interfere with the ease of absorption and hydrolysis of mustard vapor, several experiments were carried out with distilled water and with "sea" water, each contaminated with five drops of light lubricating oil per 100 cc. The suspensions were agitated thoroughly before withdrawing a 1.0-cc. sample to add to the mustard vapor. The results, also summarized in Table VI, indicate that the oil film considerably increased the rate of disappearance of I in contact with distilled water but had only a slight effect with "sea" water. The increased rate of disappearance is undoubtedly due to the much greater solubility and hence much greater rate of absorption of I in oil than in water.

SUMMARY

The "thiosulfate demand" of β-chloroethyl sulfide offers a convenient method for analysis in dilute aqueous solution.

There is no measurable hydrolysis of β-chloroethyl sulfide vapor in moist air but it is absorbed and hydrolyzed by liquid water.

URBANA, ILL.

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

HYDROLYSIS AND OXIDATION OF MUSTARD GAS AND RELATED COMPOUNDS IN AQUEOUS SOLUTION[1]

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In order to evaluate more accurately the problems involved in treatment of water contaminated with mustard gas, (β-chloroethyl sulfide, I), the behavior of I and its principal hydrolysis products, thiodiglycol (X) and the sulfonium salt XIV, toward such reagents as hypochlorite, chloramine-T, Halazone (XVII), ozone, and hydrogen peroxide was investigated, especially in dilute bicarbonate-buffered solution. The various transformations by oxidation, hydrolysis, and dehydrohalogenation outlined in the scheme on page 239 were established.

Compounds XV and XVI, the dinitrobenzoates of X and XI, and the diacetate of XII have not been previously reported. The sulfone sulfonium salt XVI was obtained only as an intractable oil, difficult to purify and characterize. Potassium mercuric iodide was found to be a sensitive reagent for detecting the three sulfonium salts (XIV, XV, and XVI). Using this test, the extent of formation of XIV from hydrolysis of I under various conditions was estimated.

It was found that Levinstein mustard[4] was considerably more resistant to dissolution in water than pure I. An investigation of residues from these experiments revealed that, whereas Levinstein mustard undergoes considerable decomposition on vacuum distillation, water-washed material distilled satisfactorily to yield water-white, stable, nearly odorless material. Exhaustive water-washing, however, left a dark, water-insoluble oily residue containing no β-chloroethyl sulfide and consisting of about 20% of the original Levinstein mustard. This material has been carefully investigated by Fuson and coworkers (1) and shown to consist of β-chloroethyl polysulfides. The reaction of three of these, the di-, tri-, and penta-sulfides, with aqueous chloramine-T at *p*H 1 led to quantitative cleavage to β-chloroethanesulfonic acid (and sulfuric acid).

$$(\mathrm{ClCH_2CH_2})_2\mathrm{S_x} \xrightarrow[\mathrm{H_2O}]{(\mathrm{O})} 2\mathrm{ClCH_2CH_2SO_3H} + (\mathrm{x} - 2)\mathrm{H_2SO_4}$$

$$(\mathrm{x} = 2, 3, 5)$$

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[1] The work reported herein was carried out under a contract, recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the University of Illinois.

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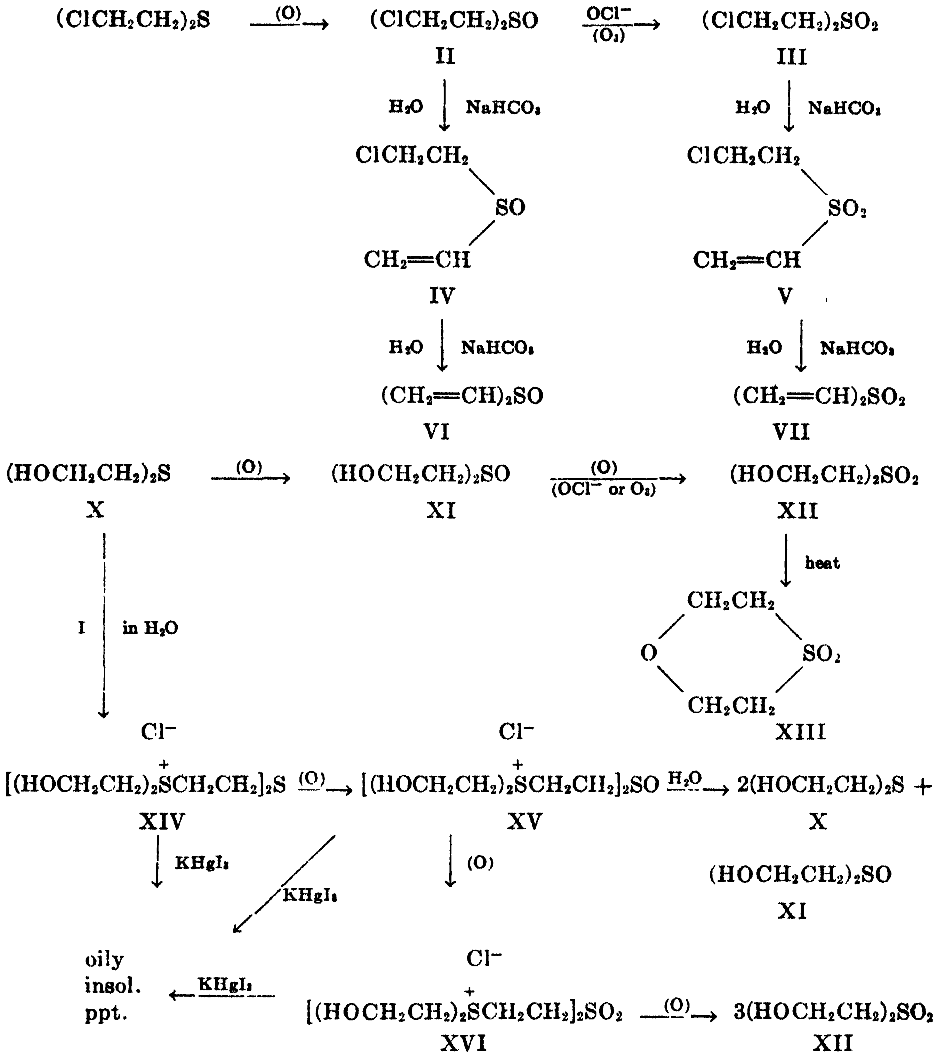
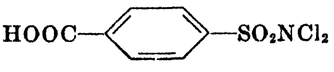
[4] Prepared by the reaction of ethylene with sulfur monochloride; supplied by the Chemical Warfare Service.

EXPERIMENTAL

Ozonization of β-chloroethyl sulfide in water. To 400 ml. of water, through which oxygen containing about two per cent ozone was being bubbled, 40 ml. of Cellosolve containing 1.6 ml. of β-chloroethyl sulfide was added dropwise during one hour. On evaporation of the water solution to dryness and recrystallization of the residue from ethanol, 1.2 g. (53%) of crystalline β-chloroethyl sulfoxide melting at 105–108° was obtained [lit. (2), 109.5°]. The melting point of a mixture with a sample of β-hydroxyethyl sulfoxide was below 95°.





Halazone, XVII

Reaction of β-chloroethyl sulfide with dilute aqueous sodium hypochlorite. To 100 ml. of water containing 2.25 millimoles of sodium hypochlorite, adjusted to *p*H 7.5 with dilute hydrochloric acid immediately before use, was added 25 ml. of methanol containing two millimoles of β-chloroethyl sulfide. The solution became slightly warm. After standing one hour, the solution was extracted three times with 40 ml. of chloroform, the extract was dried over sodium sulfate and the solvent was removed by evaporation. There was thus obtained 0.2 g. (57%) of crystals of β-chloroethyl sulfoxide melting at 105–108°. The melting point of a mixture with a sample of β-hydroxyethyl sulfoxide was 94–100°.

Reaction of β-chloroethyl sulfide with dilute aqueous chloramine-T. To 100 ml. of water containing four millimoles of chloramine-T was added 50 ml. of methanol containing four millimoles of β-chloroethyl sulfide. On concentrating the solution to a small volume, 0.55 g. (83%) of crystals separated. After two recrystallizations from ethanol, these melted at 138–142° and did not depress the melting point of an authentic sample of *p*-toluenesulfonamido-β-chloroethyl sulfilimine, m.p. 139–142° [lit. (3), 144°].

Reaction of β-chloroethyl sulfide with dilute aqueous Halazone. A solution of Halazone was prepared by dissolving the solid reagent in aqueous alkali. A 100-ml. portion of this solution, containing two millimoles of chlorine, was adjusted to *p*H 7 with dilute hydrochloric acid, and two millimoles of β-chloroethyl sulfide dissolved in 25 ml. of methanol was added. After ten minutes the solution was neutralized with excess sodium bicarbonate and then evaporated to dryness under reduced pressure. The solid residue was extracted with ether. Evaporation of the ether solution gave crystals which were recrystallized from ethanol to give 0.14 g. (40%) of β-chloroethyl sulfoxide melting at 104–107°. The melting point of a mixture with an authentic sample of β-chloroethyl sulfoxide was 105–108°.

Decomposition of β-chloroethyl sulfoxide in alkaline solution. A 2% aqueous solution of β-chloroethyl sulfoxide was prepared in distilled water. To 100 ml. of the filtered solution was added 3 g. of solid sodium bicarbonate, which was dissolved by shaking. Almost immediately, crystals of the sulfoxide began to separate from the solution. It was estimated that about half of the original amount precipitated, but the solid was not removed. Within five minutes a portion of the solution was acidified with dilute nitric acid, and a few drops of silver nitrate solution added. No trace of silver chloride was detected. After two hours, a repetition of the test gave a very faint cloudiness. After twenty-four hours the test was definitely positive with a flocculent precipitate of silver chloride forming.[5] After two weeks the original solution in distilled water still gave no test for chloride ion.

Reaction of β-chloroethyl sulfoxide with aqueous sodium hypochlorite. I. To 10 g. (57 m.moles) of β-chloroethyl sulfoxide in one liter of water containing 5 g. of sodium bicarbonate was added 300 ml. of a solution containing 114 millimoles of sodium hypochlorite adjusted to *p*H 7 with dilute hydrochloric acid immediately before use. After the solution had been allowed to stand overnight, it was extracted three times with 250 ml. of ether. The ether extracts were combined, dried over magnesium sulfate, and the ether removed by distillation. The residual oil solidified on standing, after the last traces of ether had been removed *in vacuo*. Recrystallization from ethanol gave four grams (37%) of β-chloroethyl sulfone melting at 54–56° [lit. (2), 56°].

II. Two hundred grams (1.4 moles) of β-chloroethyl sulfoxide was dissolved in 7.5 l. of water. Into this solution, 4.5 l. of 0.612 *N* sodium hypochlorite solution (1.38 moles), to which 100 g. of sodium bicarbonate had just been added, was poured rapidly with stirring. Another 100 g. of sodium bicarbonate was then added. After the reaction mixture had stood overnight, it was continuously extracted with chloroform for two days.

When the solvent had been removed at water-pump pressure, the residual liquid (205 g.) rapidly precipitated a large mass of crystals. Filtration gave 167 g. of liquid, 37 g. of solid. The melting point of the solid was 103–107°, that of β-chloroethyl sulfoxide.

The filtrate was subjected to a rapid vacuum distillation from a Claisen flask, b.p.

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[5] In contrast to the stability reported by Marshall and Williams (4a) and Peters and Walker (4b).

73–145° (1.0 mm.), leaving a black semi-solid residue of 30 g. from which 9 g. of light tan crystals, melting at 107–108° were obtained by washing with acetone. The distillate was then fractionally redistilled through a 12-inch column packed with Berl saddles. The results, summarized in Table I, indicate the presence of vinyl sulfoxide [b.p. 81° (16 mm.); n_D^{20} 1.5100] and sulfone [b.p. 109° (16 mm.); n_D^{20} 1.4782], and β-chloroethyl vinyl sulfoxide [b.p. 126° (15 mm.); n_D^{20} 1.5232] and sulfone [b.p. 143° (16 mm.); n_D^{20} 1.4952] (5,6).

The solubility of β-chloroethyl sulfone in water. A sample of β-chloroethyl sulfone was recrystallized repeatedly from ethanol until it failed to give a precipitate with alcoholic silver nitrate, m.p. 55.0–55.2°. About ten grams of this sample was placed in a glass-stoppered bottle containing 700 ml. of distilled water. The bottle was kept in a constant temperature bath at 25° for seven days. At intervals it was removed and thoroughly shaken. At the end of this time the solution gave no test for chloride ion with silver nitrate, and there was still some undissolved sulfone in contact with the solution. Samples of the solution were then transferred to tared weighing bottles; the bottles were weighed and the water was then allowed to evaporate in a desiccator over calcium chloride. The bottles were dried to constant weight and the amount of sulfone in a given amount of water thus determined by difference. The melting point of the sulfone recovered from this experiment was 54–55°, with slight softening at 50°. A blank experiment in which weighed amounts of sulfone were placed in the weighing bottles, water added, the water evaporated as above, and the sulfone reweighed, showed that no sulfone was lost by this method. The solubility of the sulfone as determined in this way was 1.115 g. in 100 g. of water. This is about twice that reported by Helferich and Reid (2). After seventeen days the saturated solution still contained no chloride ion as shown by a silver nitrate test.

TABLE I

DISTILLATION OF CHLORINATED β-CHLOROETHYL SULFOXIDE

WEIGHT IN GRAMS	BOILING POINT, °C.	PRESSURE IN MM.	n_D^{20}
2.05	57–53	0.13	1.5040
3.05	53–52	.08	1.4984
3 15	53–57	.08	1.4978
2.00	58–70	.12	1.5053
2.25	70–84	.22	1.5152
2.50	83–86	.26	1.5182
3.45	82–88	.33	1.5078
4 90	88–89	.33	1.5007
5.35	91	.30	1.4992
9.25	84	.25	1.4972
9.30	83	.18	1.4968
6.80	81–82	.16	1.4962
6 25	79–81	.14	1.4962
3.65	81	.17	1.4962
5.45	89–91	.26	1.4977

Decomposition of β-chloroethyl sulfone in alkaline solution. When a 1% solution of β-chloroethyl sulfone in distilled water was made alkaline to *p*H 7.8 by the addition of sodium bicarbonate, the solution gave a precipitate of silver chloride within five minutes, while the original solution, *p*H 5.5, did not give a similar precipitate after two weeks.

To a solution of 10 g. (0.052 m.) of β-chloroethyl sulfone in a liter of water was added 16.8 g. (0.2 m.) of sodium bicarbonate. After standing overnight, the solution gave a positive test for unsaturation with potassium permanganate and with bromine in carbon tetrachloride. The solution was extracted with ether in a continuous liquid-liquid extractor for sixteen hours. Evaporation of the ether solution gave two grams of residual oil. Distillation of this material gave 1.6 g. of vinyl sulfone, boiling at 110° (17 mm.); n_D^{20} 1.4750 [lit. (6), b. p. 109° (16 mm.); n_D^{20} 1.4782].

The preparation of β-hydroxyethyl sulfone. Following the procedure of Gilman and Beaber (7), 5 g. (0.04 mole) of thiodiglycol was dissolved in 10 ml. of glacial acetic acid, and 11.5 g. (0.1 mole) of 30% hydrogen peroxide was added slowly in the cold with stirring. The resulting mixture was then heated on the steam-bath for two hours, after which the solvent was removed by distillation at reduced pressure. An oil was thus obtained which would not crystallize on cooling, drying over phosphorus pentoxide, or rubbing under various solvents. An attempted distillation of this material gave an oil boiling at 130–140° (1 mm.), which solidified on cooling and, after recrystallization from butanol, melted at 129–130°. The melting point and analysis indicated this to be thioxane sulfone [lit. (8), m.p. 130°].

Anal. Calc'd for $C_4H_8O_3S$: C, 35.30; H, 5.88.

Found: C, 35.50; H, 6.36.

Crystallization of the undistilled oil could not be induced by seeding with thioxane sulfone.

The method of Lewin (5) was then followed to obtain crystalline β-hydroxyethyl sulfone. Perbenzoic acid was prepared as a 0.51 *M* solution in ether using the procedure in Organic Syntheses. A mixture of 100 ml. of absolute ethanol, 80 ml. of chloroform and 5 g. (0.04 mole) of thiodiglycol was cooled to −5° and 200 ml. (0.1 mole) of the perbenzoic acid solution was added. After allowing the solution to stand for twenty hours, the solvents were removed by evaporation at reduced pressure. The residue was taken up in ether and cooled in a dry ice-acetone bath until crystals were obtained. After three recrystallizations from ether, the melting point was 54–55°. When the oil prepared from the hydrogen peroxide method was rubbed under ether or acetone and seeded with crystals from the perbenzoic acid reaction, crystallization finally occurred. It was found more convenient to use acetone for recrystallization, since cooling to 0° was then sufficient, but seeding was always found necessary with this solvent. The compound was rather difficult to purify in any case, and the melting point reported by Lewin [57–58° (5)] was never attained.

Ozonization of thiodiglycol in water. Oxygen containing 2.5% ozone was bubbled through 100 ml. of water containing 1.6 g. (0.013 mole) of thiodiglycol for ninety minutes at a rate of 200 ml. of oxygen a minute. Thus 0.02 mole of ozone was passed into the solution. On evaporating the water and drying the residue in a desiccator over phosphorus pentoxide, 1.7 g. (95% yield) of slightly oily crystals were obtained. After one recrystallization from *n*-butanol, the melting point and the melting point of a mixture with an authentic sample of β-hydroxyethyl sulfoxide were both 106–108° [lit. (5), 112°].

A solution of 4.7 g. (0.031 mole) of β-hydroxyethyl sulfoxide in 200 ml. of water was treated with 0.65% ozone at one liter per minute for three hours, thus applying 1.5 moles of ozone per mole of sulfoxide. The solution was then evaporated to dryness leaving a crystalline residue which was extracted with three 10-ml. portions of acetone. There then remained 3.3 g. of material, melting point and melting point mixed with an authentic sample of β-hydroxyethyl sulfoxide, 105–108°. The acetone was removed by evaporation leaving an oil which solidified on rubbing under dry ether to give 1.0 g. of crude β-hydroxyethyl sulfone melting at 36–43°, a conversion of 20% and a yield of 64% based on unrecovered starting material. After one recrystallization from acetone, the melting point was 50–54°.

Reaction of thiodiglycol with dilute aqueous chloramine-T. To 375 ml. of water containing 3 g. (0.025 mole) of thiodiglycol buffered to *p*H 6.9 was added 0.025 mole of chloramine-T in 100 ml. of water. On partial evaporation of the resulting solution, about one gram of solid separated and was removed by filtration. The melting point was 133–135° (lit. for *p*-toluenesulfonamide, 137°). The solution was then evaporated to dryness and the solid residue extracted with hot butanol. On cooling, 1.7 g. (50% yield) of crystals of β-hydroxyethyl sulfoxide separated from the butanol. The melting point and melting point of a mixture with an authentic sample were 108°.

Reaction of thiodiglycol with dilute aqueous Halazone. To 10 ml. of water containing 4.28

millimoles of thiodiglycol was added 100 ml. of water containing 4.28 millimoles of chlorine as Halazone. The Halazone solution had been made up from solid Halazone and dilute alkali and was acidified with dilute hydrochloric acid to *p*H 7 immediately before use. The solution was concentrated to a small volume by evaporation at reduced pressure and acidified. The *p*-sulfamylbenzoic acid which precipitated was removed by filtration. The solution was then evaporated to dryness and the solid residue extracted with hot butanol. On cooling the solution, 0.45 g. (76% yield) of crystalline β-hydroxyethyl sulfoxide separated. The melting point and melting point of a mixture with an authentic sample were 106–108°.

Reaction of thiodiglycol with dilute aqueous sodium hypochlorite. To 1.65 g. (14.4 m.moles) of thiodiglycol was added 200 ml. of 0.1444 *N* sodium hypochlorite solution (14.4 m.moles). The hypochlorite was prepared by passing chlorine into a solution of sodium hydroxide, standardized by titration of the iodine liberated by an aliquot with standard sodium thiosulfate, and adjusted to *p*H 7 with dilute hydrochloric acid immediately before use. The resulting solution was neutralized with excess sodium bicarbonate and then evaporated to dryness at reduced pressure. The residue was extracted with hot butanol. On cooling the butanol solution, 1.2 g. (60% yield) of crystals were obtained. The melting point and melting point of a mixture with β-hydroxyethyl sulfoxide were 106–108°.

Solutions of thiodiglycol containing from one to ten grams of glycol per 100 ml. of solution were treated with chlorine both by bubbling in an excess of chlorine and by adding an excess of neutral sodium hypochlorite solution as prepared above. In every case the reaction proceeded vigorously with the evolution of appreciable heat in the more concentrated solutions. Neutralization of the solutions with sodium bicarbonate, followed by evaporation at reduced pressure, extraction of the residue with dioxane, and evaporation of the dioxane gave oils from which thioxane sulfone was obtained in good yields by distillation, as described in the preparation of β-hydroxyethyl sulfone.

A test for the sulfonium salt (XIV) in water. Stock solutions of chloroplatinic acid, chlorauric acid, mercuric chloride, mercuric iodide, and picric acid in water were used. A few drops of each reagent were added to aliquots of successive dilutions of the sulfonium salt (9) in water. By observing the dilution at which the insoluble solid or oil, formed by the addition of the reagent, was just barely detectable, it was found that the complex formed with mercuric iodide was the least soluble and therefore most suited for development as an identifying test. A solution prepared from 26 g. of potassium iodide, 45 g. of mercuric iodide, and 20 ml. of water was used in subsequent tests. The addition of 0.02 ml. of this solution to 2 ml. of the solution being tested gives a noticeable white cloudiness in the presence of 10 mg./liter of the sulfonium salt in water. A solution containing 5 mg./liter did not give a positive test under these conditions. It is important that the results of the test be observed within five or ten seconds after addition of the reagent and that the cloudiness be creamy white, since addition of the reagent to distilled water produces a reddish-gold crystalline precipitate after about thirty seconds.

Formation of sulfonium salts during the hydrolysis of β-chloroethyl sulfide. One hundred milliliters of distilled water and 0.64 g. of β-chloroethyl sulfide were shaken together in a glass-stoppered flask until complete solution had occurred. A sample of the resulting solution was diluted until it just gave a positive test for the sulfonium salt with the potassium mercuric iodide reagent. The dilution factor of the most dilute solution to give a test was 100. The original solution therefore contained about 1000 mg. of the sulfonium salt per liter. Thus about 16% of the β-chloroethyl sulfide was converted to sulfonium salts.

The experiment was repeated using a phosphate buffered solution, the *p*H of which fell from 7.3 to 6.4 during the experiment, and also using a bicarbonate-buffered solution in which the *p*H fell from 7.9 to 7.4. In the first case, the original solution gave no test for the sulfonium salt while in the latter the dilution factor was 30. Thus there was less than 0.1% sulfonium salt formation in the first case and about 5% in the second.

Preparation of the sulfonium salt sulfoxide (XV). To 20 g. (0.05 mole) of the sulfonium salt (9) was added 5.7 g. (0.05 mole) of 30% hydrogen peroxide. The mixture was stirred until complete solution occurred and then poured into an evaporating dish. Water was first evaporated in a stream of dry air, then over calcium chloride, and the last traces of moisture removed in a vacuum desiccator over phosphorus pentoxide. After standing several weeks in the desiccator, the compound finally solidified to a yellowish mass of crystals. The material was so strongly deliquescent that it could not be dried by means of calcium chloride. Purification had to be carried out in an atmosphere dried over phosphorus pentoxide.

The salt was insoluble in all ordinary solvents except water and methanol. It was recrystallized by dissolving in a small amount of methanol, adding absolute ethanol to incipient cloudiness, and then chilling the solution in an icebox for several days. Rosettes of needle-like crystals first formed on the sides of the flask and then spread throughout the solution. After two recrystallizations, the melting point in a sealed tube was 63.5–65°.

Anal. Calc'd for $C_{12}H_{28}Cl_2O_5S_3$: C, 34.28; H, 6.68.

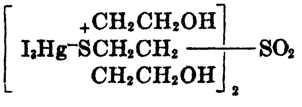
Found: C, 34.92; H, 6.74.

An attempt was made to prepare this compound by heating one equivalent of β-chloroethyl sulfoxide with three of thiodiglycol for six hours at 75°. However, on cooling the oil which had formed, the original sulfoxide recrystallized. The mixture was completely soluble in chloroform, indicating that no salts had been formed.

Oxidation of the sulfonium salt (XIV) with chloramine-T. To 8.8 g. (0.022 mole) of the sulfonium salt in 50 ml. of water was added slowly with stirring 100 ml. of water containing 0.022 mole of chloramine-T. When about 30 ml. had been added a precipitate began to form. After all the chloramine-T had been added, stirring was continued for one hour. The precipitate was removed by filtration and dried over calcium chloride. There was thus obtained 3.5 g. (92% yield) of crystals melting at 123–124°. Recrystallization from benzene and then from ethanol raised the melting point to 135–136°. A mixture with an authentic sample of *p*-toluenesulfonamide (m.p. 133–134°) melted at 133–134°. The yield of crude amide indicated that no sulfilimine had been formed. Isolation of the sulfoxide of the sulfonium salt from the water solution was not attempted, since the properties of the compound made success seem unlikely.

Preparation of the sulfonium salt sulfone (XVI). A 20 g. (0.05 mole) sample of the sulfonium salt XIV was dissolved in a small amount of water and 17 g. (0.15 mole) of 30% hydrogen peroxide was added. The solution was evaporated in a stream of dry air until no further loss in weight occurred; the resulting oil was then dried in a vacuum desiccator containing phosphorus pentoxide at a pressure of one millimeter until no further evolution of gas was observed and constant weight was attained. The liquid residue was completely insoluble in chloroform, showing that decomposition of the sulfonium salt had not taken place. The oil was soluble only in methanol and water, was not hygroscopic, and did not crystallize on prolonged cooling in dry ice or liquid air accompanied by rubbing under various anhydrous solvents. Crystals of the sulfoxide of the sulfonium salt, instead of causing the oil to crystallize, readily dissolved in it.

A solution of 5 ml. of water containing 1.5 g. of the oil was treated with an excess of potassium mercuric iodide solution. A heavy oil precipitated which was washed successively with potassium iodide solution, two portions of water, then ethanol. The residual oil was dried to constant weight *in vacuo* over phosphorus pentoxide. There was thus obtained 3.2 g. of a honey-like oil, a 97% yield assuming the oil to be



$$\left[I_3Hg^{-}\overset{+CH_2CH_2OH}{\underset{CH_2CH_2OH}{S}}CH_2CH_2-\right]_2SO_2$$

Attempted preparation of derivatives of the sulfone of the sulfonium salt by the addition of aqueous solutions of chloroplatinic acid, chlorauric acid, mercuric chloride, and picric acid to the sulfone led in every case to the formation of insoluble oils which did not crystallize.

Preparation of 2-(3,5-dinitrobenzoxy)ethyl sulfide and sulfoxide. A solution of 1 g. of thiodiglycol was shaken with 4 g. of 3,5-dinitrobenzoyl chloride while 0.7 g. of sodium hydroxide in 10 ml. of water was added in small portions. The precipitate which formed was recrystallized several times from a mixture of ethanol and benzene. The melting point of the final product was 161–162°.

Anal. Calc'd for $C_{18}H_{14}N_4O_{12}S$: C, 42.35; H, 2.74.
Found: C, 42.77; H, 2.97.

The corresponding derivative of the sulfoxide was prepared by the same procedure. The material was recrystallized from butanol, m.p. 185–186°.

Anal. Calc'd for $C_{18}H_{14}N_4O_{13}S$: C, 41.07; H, 2.67; S, 6.08.
Found: C, 41.35; H, 2.79; S, 5.67.

TABLE II

DISTILLATION OF β-CHLOROETHYL DISULFIDE FROM WATER-WASHED LEVINSTEIN MUSTARD

WEIGHT IN GRAMS	B.P., (2 MM.) °C	n^{20}
2.80	41–57	1.5755
0.90	57	1.5769
4.65	61	1.5365
6.05	60–65	1.5291
4.90	65–87	1.5352
7.85	91	1.5602
7.55	92	1.5657
8.60	91	1.5660
8.65	92	1.5659
8.45	92	1.5660
9.00	90	1.5659
8.40	89	1.5658
5.65	91–95	1.5659
3.95	94–98	1.5666
6.55	101–106	1.5673
7.30	105–118	1.5697
6.60	106–111	1 5688
1.05	111	1.5683

bis-β-Hydroxyethyl sulfone diacetate. The oil resulting from the oxidation of 10 g. of thiodiglycol with an excess of 30% hydrogen peroxide according to Gilman and Beaber (7) was treated with an excess of acetic anhydride, added dropwise. A vigorous reaction occurred and the solution became slightly discolored. After evaporation of acetic acid, the oil was subjected to vacuum distillation in a Claisen flask. The fraction boiling at 170–190° (2 mm.) was redistilled twice through a small column and a fraction obtained boiling at 175° (2 mm.). In distillation, small amounts of thioxane sulfone (m.p. 130°) separated from the main fraction as an immiscible oil which solidified on cooling. This was removed by filtration before redistillation and from the final product before analysis.

Anal. Calc'd for $C_8H_{14}O_6S$: C, 40.33; H, 5.88; S, 13.57; Sap. eq., 119.1.
Found: C, 39.90; H, 5.97; S, 13.28; Sap. eq., 121.4.

It is interesting to note that, in measurement of the saponification equivalent, the diacetate was saponified instantly by cold dilute aqueous alkali. This ease of saponification is analogous to the case of dehydrohalogenation of β-chloroethyl sulfone by alkali. It also probably explains why all attempts to prepare the *bis*-3,5-dinitrobenzoate of the sulfone (XIII) failed, since these attempts all involved either preparation in the presence of alkali or washing with alkali.

Distillation of water-washed Levinstein mustard. An eleven-hundred-gram sample of Levinstein mustard was stirred in a 5-l. flask with fresh portions of water until the residue weighed 892 g. This was then distilled from a Claisen flask at reduced pressure. There was first distilled 620 g. (69.5%) of water-white, nearly odorless material boiling at 59° (1 mm.), n_{D}^{20} 1.5281, having a refractive index close to that of pure β-chloroethyl sulfide, n_{D}^{20} 1.5273 (1). The odor and color did not change on standing in glass exposed to light. Following this distillate there was obtained 163 g. of a yellow liquid boiling at 59–120° (1–4 mm.) and having a foul odor. Considerable decomposition occurred in the pot during this part of the distillation.

TABLE III

DISTILLATION OF LEVINSTEIN MUSTARD

WEIGHT IN GRAMS	B.P., °C	PRESSURE IN MM.	n_{D}^{20}
228	57	0.13	1.5273
204	57	0.13	1.5278
89	58–59	0.25–0.35	1.5287
20	59–64	0.35–0.55	1.5308
59	71–90	0.55–1.1	1.5441

TABLE IV

DISSOLUTION OF LEVINSTEIN MUSTARD BY SHAKING WITH WATER AT ROOM TEMPERATURE

CC. LEV.	CC. H_2O	Cl^- FORMED			% I IN LEV. (Cl^-)	CC. OF INSOL. RESIDUE	% I IN LEV. (RESIDUE)	XIV (PPM IN H_2O)
		2 days	5 days	14 days				
6.8	294	0.102	0.093	0.096	80.3	1.0	85	3300
15	285	.195	.192	.189	75.2	2.8	81	9600
30	270	.248	.353	.371	73.8	5.8	81	43,200
60	240	.285	.45	.782	77.7	12.0	80	48,000

The 163-g. sample was redistilled through a column packed with Berl saddles. The results, summarized in Table II, indicate that 80 g. of the 110 g. distilled was fairly pure β-chloroethyl disulfide (1).

From the first two fractions taken, a small amount of solid separated on cooling. Two recrystallizations from ether gave 0.08 g. melting at 110–111°. Pure dithiane melts at 112° (10).

Distillation of unwashed Levinstein mustard. Seven hundred seventy-five grams of Levinstein mustard was distilled at reduced pressure from a one-liter Claisen flask. There was noticeable decomposition with the evolution of gases throughout the distillation, increasing as the bath temperature increased. The results are summarized in Table III. The distillate was all yellow-brown, with the higher-boiling fractions somewhat darker than the others. The odor of each fraction was a mixture of β-chloroethyl sulfide and hydrogen chloride. Significantly, there was no foul odor in the last fraction corresponding to that found in distillates from water-washed Levinstein mustard.

Persistence of Levinstein mustard in water. Four mixtures of water and Levinstein mustard in glass-stoppered Erlenmeyer flasks were placed on a shaking machine. Two cubic centimeter samples of water were withdrawn periodically and the chloride ion titrated by the Volhard method. At the end of the experiment, the volume of insoluble black oil (n_D^{20} 1.74) was measured. The results are tabulated below (Table IV). Assuming β-chloroethyl sulfide (I) to be the only substance reacting and dissolving, the per cent of I in the Levinstein was calculated both from the chloride ion liberated and from the volume of the insoluble residue. Results of potassium mercuric iodide tests for the amount of sulfonium salt XIV formed are also included in the table.

The reaction of β-chloroethyl di-, tri-, and penta-sulfides with aqueous chloramine-T. Dioxane was added to 0.185 g. (0.968 millimole) of β-chloroethyl disulfide (1), 0.138 g. (0.618 millimole) of β-chloroethyl trisulfide (1), and 0.132 g. (0 460 millimole) of β-chloroethyl pentasulfide (1) to make 50.0 ml. of solution in each case. Each standard solution was used in turn in the following procedure. To 100 ml. of 0.034 *N* aqueous chloramine-T solution was added 5.0 ml. of the standard dioxane solution. After 30 seconds, 5 ml. of concentrated hydrochloric acid was added. At the end of a known time interval, an excess of solid potassium iodide was added and the liberated iodine titrated with 0.0224 *N* sodium thiosulfate. The amount of chloramine-T consumed was then calculated. The results are summarized in Table V.

TABLE V

CHLORINE DEMAND OF β-CHLOROETHYL DISULFIDE, TRISULFIDE, AND PENTASULFIDE

TIME IN MINUTES	MOLES × 10^{-3} CHL.-T CONSUMED	MOLE-RATIO OF CHL.-T TO SULFIDE
	β-Chloroethyl Disulfide	
15	0.368	3.8
35	.458	4.7
55	.483	5.0
95	.503	5.2
	β-Chloroethyl Trisulfide	
10	0.421	6.8
25	.477	7.7
35	.488	7.9
50	.491	7.9
70	.497	8.0
	β-Chloroethyl Pentasulfide	
10	0.557	12.1
15	.586	12.7
30	.619	13.4
45	.626	13.6
70	.632	13.7

SUMMARY

An investigation of the hydrolysis and oxidation of β-chloroethyl sulfide, undertaken to evaluate its hazards as a water contaminant, has established a number of hydrolytic and oxidative transformations in aqueous solution.

URBANA, ILL.

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE HYDROLYSIS AND OXIDATION OF β-(β′-CHLOROETHYLTHIO)-ETHYL ETHER AND RELATED COMPOUNDS[1]

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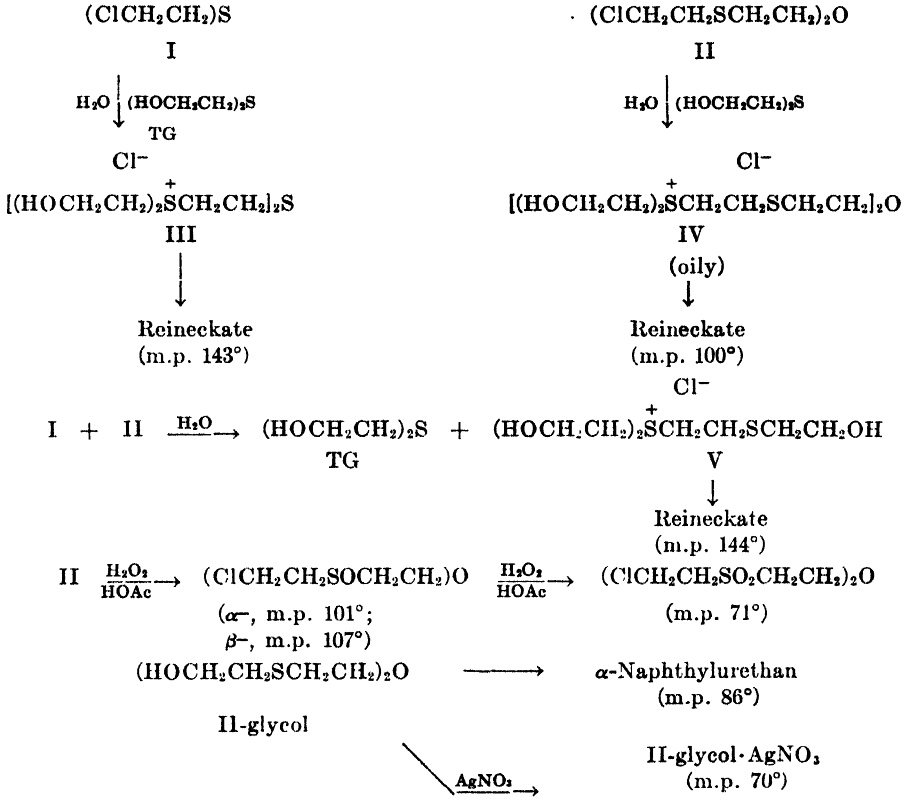
Various transformations of an analog of β-chloroethyl sulfide (I), β-(β′-chloroethylthio)ethyl ether (II), have been investigated and are summarized in the chart below.



$$(ClCH_2CH_2)S\ \text{(I)} \xrightarrow[\text{TG}]{H_2O \,|\, (HOCH_2CH_2)_2S} [(HOCH_2CH_2)_2\overset{+}{S}CH_2CH_2]_2S\ \overset{Cl^-}{}\ \text{(III)} \longrightarrow \text{Reineckate (m.p. 143°)}$$

$$(ClCH_2CH_2SCH_2CH_2)_2O\ \text{(II)} \xrightarrow{H_2O \,|\, (HOCH_2CH_2)_2S} [(HOCH_2CH_2)_2\overset{+}{S}CH_2CH_2SCH_2CH_2]_2O\ \overset{Cl^-}{}\ \text{(IV) (oily)} \longrightarrow \text{Reineckate (m.p. 100°)}$$

$$\text{I} + \text{II} \xrightarrow{H_2O} \underset{\text{TG}}{(HOCH_2CH_2)_2S} + \underset{\text{V}}{(HOCH_2CH_2)_2\overset{+}{S}CH_2CH_2SCH_2CH_2OH}\ \overset{Cl^-}{} \longrightarrow \text{Reineckate (m.p. 144°)}$$

$$\text{II} \xrightarrow[HOAc]{H_2O_2} \underset{(\alpha\text{-, m.p. 101°; } \beta\text{-, m.p. 107°)}}{(ClCH_2CH_2SOCH_2CH_2)O} \xrightarrow[HOAc]{H_2O_2} \underset{\text{(m.p. 71°)}}{(ClCH_2CH_2SO_2CH_2CH_2)_2O}$$

$$\underset{\text{II-glycol}}{(HOCH_2CH_2SCH_2CH_2)_2O} \longrightarrow \alpha\text{-Naphthylurethan (m.p. 86°)}$$

$$\text{II-glycol} \xrightarrow{AgNO_3} \text{II-glycol}\cdot AgNO_3\ \text{(m.p. 70°)}$$

EXPERIMENTAL

Hydrolysis of β-(β′-chloroethylthio)ethyl ether (II). A mixture of 10.1 g. (0.0386 mole) of II and 1000 cc. of water was shaken on a mechanical shaker. A cloudy solution resulted after ten hours. Attempts to analyze this ten-hour hydrolysate for chloride ion by the Volhard procedure failed. The end points were poor and the values for chloride were greater than the theoretical amount. Mohr's method using chromate and Fajan's method using dichlorofluorescein were also unsatisfactory. Investigation disclosed that β-(β'-hydroxyethylthio)ethyl ether (II-glycol) interfered with the chloride determination since a salt was formed between one mole of the glycol and one mole of silver nitrate (see below).

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The acid liberated at various times was determined by titration of an aliquot portion with standard sodium hydroxide using phenolphthalein for the end point. These data, illustrated graphically in Fig. 1, reveal a rapid liberation of about two-thirds of the expected acid followed by a much slower liberation of the remaining acid. The kinetics indicate that this latter slow liberation of acid, undoubtedly from hydrolysis of sulfonium salts, is a first-order reaction with a half-life of 3.4 days. Evidently approximately one-third of the original chloroethyl groups were rapidly converted to sulfonium salt groups which subsequently underwent a slower hydrolysis.

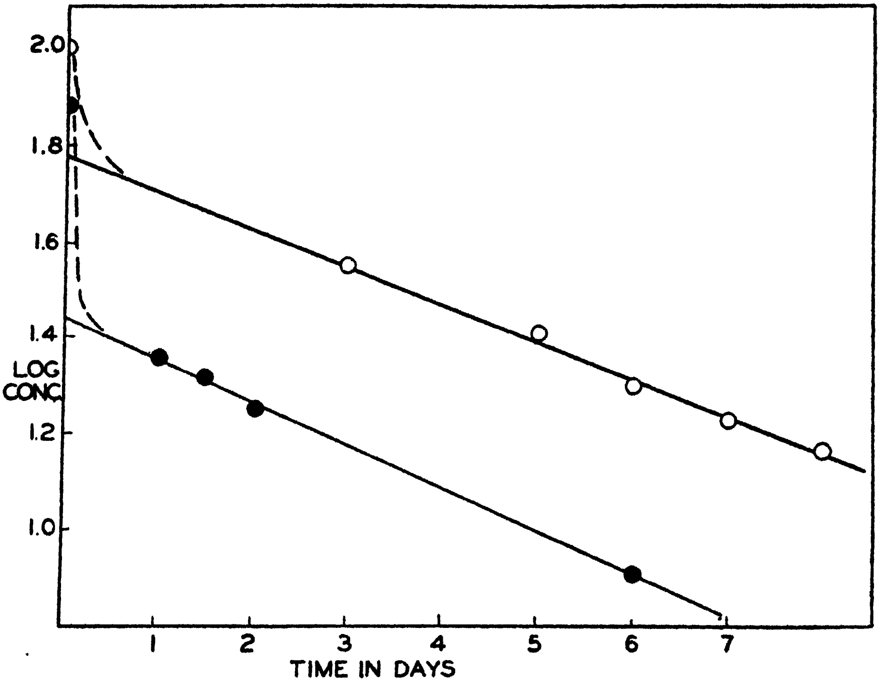

Fig. 1. Kinetics of Hydrolysis of Sulfonium Salts from II. ○; II·2TG (IV). $t_{1/2}$ = 3.8 days: ●; II Hydrolysate, $t_{1/2}$ = 3.4 days.

The five-minute chlorine demand of a one-to-ten dilution of the ten-hour hydrolysis solution was determined at *p*H 7 using hypochlorite with acetate buffer. It was found that 4.09 moles of chlorine had been consumed per mole of II. This is in agreement with the observation that, under these conditions, the sulfonium salt formed from β-chloroethyl sulfide and thiodiglycol is cleaved to give the theoretical chlorine demand for *all* the sulfur atoms.

In another experiment, 12.05 g. (0.0458 mole) of II and 1000 cc. of water were shaken mechanically overnight. The resulting solution, *p*H 1.5, gave an instantaneous creamy precipitate with potassium mercuric iodide (1). A 25-cc. aliquot was added to 0.2 g. of sodium picrylsulfonate in 10 cc. of 0.5 *N* hydrochloric acid to yield an oil which resisted all attempts at crystallization. The thiosulfate demand was determined by adding an excess of thiosulfate to an aliquot portion, after the *p*H had been raised to approximately 6 by addition of sufficient 2% sodium bicarbonate. After eighteen hours, the solution was found to have consumed one mole of thiosulfate per 3.18 moles of II used to prepare the solution. On the basis that one-third of the initial chloroethyl groups were converted to sulfonium salt groups, this corresponds to 50% reaction of the latter with thiosulfate in twenty-four hours. This is the same rate as that observed for IV (see below) and is considerably more rapid than the half-life for III of three days at 37° or ten days at 25° (2).

All attempts to isolate products from these hydrolyses yielded only oils which appeared to be mixtures, principally of various sulfonium salts. These oils were soluble in water and in chloroform, relatively insoluble in acetone, gave instantaneous precipitates with silver nitrate, di-α-naphthylurea on treatment with α-naphthyl isocyanate and, in general resisted purification or identification.

Reaction of II with thiodiglycol. The examination of solutions from the hydrolysis of II indicated the presence of oily sulfonium compounds in the reaction products. Since no solid compounds or derivatives could be obtained, the sulfonium salt from condensation of II with two moles of thiodiglycol, compound IV, was prepared in order to study its properties.[4] A mixture of 13.2 g. (0.05 mole) of II and 18.3 g. (0.15 mole) of thiodiglycol dissolved in 200 cc. of water was stirred at room temperature. After twenty-three hours, a clear solution resulted. An aliquot of the solution was titrated with standard alkali using phenolphthalein for the end point. The titration showed that 0.015 equivalents of acid had been formed during the reaction (only 15% of theoretical for complete hydrolysis of II).

The solution was evaporated to dryness under diminished pressure (bath temperature 40°). The residual oil was dissolved in 100 cc. of absolute ethanol, filtered and the solution evaporated to dryness. The oil was then triturated with one 50-cc. portion of ether and two 100-cc. portions of acetone. The last traces of solvent were removed with a Hyvac pump and the pale yellow oil was dried over phosphoric anhydride *in vacuo*, weight 25.1 g. The oil could not be induced to crystallize.

A solution containing 2.740 g. of the oil in 250 cc. of water was prepared. The thiosulfate demand was determined. Enough 2% sodium bicarbonate (0.3 cc.) was added to a 10-cc. aliquot to raise the *p*H to approximately 6 and then 5 cc. of acetate buffer and excess sodium thiosulfate solution were added. After twenty-four hours the solution was found to have consumed 1.02 moles of thiosulfate per mole of sulfonium salt IV (50% based on the oil as pure IV).

The acid liberated from this solution was determined by titrating 10-cc. aliquots with sodium hydroxide at intervals. After eight days, the *p*H was about 2.0 and 1.56 moles of acid per mole of sulfonium salt IV (75% based on oil as pure IV) had been liberated. From the kinetic data, summarized graphically in Fig. 1, the half-life for hydrolysis was estimated to be 3.8 days.

Attempts to prepare a solid derivative with picric acid, picrylsulfonic acid, mercuric and cupric chlorides, potassium dichromate, perchloric acid, and chloroplatinic acid yielded only oils. The sulfonium nitrate, frequently a stable and crystalline derivative, was prepared according to Renshaw and Searle (4). It also proved to be an oil.

The *Reineckate* was a solid. A solution of 2.69 g. (0.0076 mole) of Reinecke's salt in 40 cc. of methanol was added to a solution of 2.0 g. of the oil in 40 cc. of methanol. A light pink precipitate formed immediately. The precipitate was collected on a filter and dried over phosphoric anhydride *in vacuo*, weight 2.3 g., m.p. 91–95°, dec. The compound was partially decomposed in hot Methyl Cellosolve solution. After two reprecipitations by addition of water to a cold Methyl Cellosolve solution, the compound melted at 97–100°, dec.

Anal. Calc'd for $C_{24}H_{48}Cr_2N_{12}O_5S_{12} \cdot C_3H_8O_2$: C, 28.21; H, 4.91.

Found: C, 28.36; H, 4.77.

Hydrolysis of a mixture of I and II. A suspension of 20.8 g. (0.11 mole) of a mixture consisting of 60% I and 40% II in 1500 cc. of water was shaken on a mechanical shaker for twenty-four hours. Titration of an aliquot with standard sodium hydroxide showed that 173 milliequivalents of acid had been liberated, 78.5% of the 220 milliequivalents possible. After two weeks, the acid liberated increased to 203 equivalents, 92.5% of theoretical.

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[4] See Davies and Oxford (3) for the similar preparation of III.

An 1100-cc. portion of the hydrolysis solution was neutralized with 6.0 g. (0.15 mole) of sodium hydroxide. The solution was evaporated to dryness under diminished pressure (bath temperatures 50°). The residue was extracted with 100 cc. of hot ethanol. The solid inorganic residue remaining weighed 9.0 g.; the theoretical amount of sodium chloride should be 8.8 g.

The ethanol was removed by distillation at ordinary pressure and the residual oil, 12.0 g., was distilled from a modified Claisen distilling flask under diminished pressure. There was obtained 4.2 g. of thiodiglycol, b.p. 119–120° (1.2 mm.). No more material distilled above 120° and the distillation temperature dropped while the bath temperature was raised from 195° to 221°. The residue, 6.8 g., was a light brown viscous oil.

The thiodiglycol was identified by preparation of the 3,5-dinitrobenzoate derivative (1), melting point and mixed melting point with an authentic sample, 162–164°. It was calculated that 12.8g. of mixed glycols should have been obtained from 1100 cc. of hydrolysate, 7.5 g. of which should be thiodiglycol. The yield of thiodiglycol, 4.2 g., was thus 56%.

The residue from the distillation was dissolved in 150 cc. of ether and separated from a slight amount of sodium chloride which precipitated. The oil could not be crystallized from ether, as in the case of II-glycol, or from alcohol-ether solution. The solvents were evaporated under diminished pressure to yield 6.3 g. of oil. The oil did not solidify on cooling in a Dry-Ice-acetone bath. No test for chloride was obtained with silver nitrate solution as for the oily sulfonium salts formed from hydrolysis of pure II. Two attempts at the preparation of the α-naphthylurethan resulted in an oil which could not be induced to crystallize.

A 250-cc. sample of the hydrolysate was treated with an aqueous solution of 3.0 g. of Reinecke's salt. The precipitate was dried over calcium chloride *in vacuo*, m.p. 130–135°. dec., weight 2.00 g. The Reineckate was recrystallized five times from Methyl Cellosolve-water solution, to yield less than 0.5 g. of product, m.p. 143–144°, dec. The melting point was not depressed by admixture with III Reineckate (m.p. 142–143°, dec.). The analysis, however, checked for the *Reineckate* of the sulfonium salt from β-hydroxyethyl β-chloroethyl sulfide with thiodiglycol (V).

Anal. Calc'd for $C_{12}H_{25}CrN_6O_3S_6$: C, 26.41; H, 4.62; S, 35.35.
Found: C, 26.52; H, 4.53; S, 33.74.

In another experiment the same Reineckate, m.p. 141–142°, dec , was isolated from a six-weeks-old hydrolysis solution of 60% I, 40% II and found to analyze correctly for the Reineckate of V.

Anal. Calc'd for $C_{12}H_{25}CrN_6O_3S_6$; C, 26.41; H, 4.62.
Found: C, 26.27; H, 4.46.

Preparation of the Reineckate of III. A solution of 1.0 g. (2.82 m.moles) of Reinecke's salt in 25 cc. of methanol was added to 0.5 g. (1.24 m.moles) of III (3) in 25 cc. of methanol. The precipitate was collected and dried over calcium chloride *in vacuo*, weight 1.20 g. (100%), m p. 141–142°, dec. The compound was recrystallized twice from Methyl Cellosolve-water solution in fine dark pink crystals, m.p. 142–143°, dec.

Anal. Calc'd for $C_{20}H_{40}Cr_2N_{12}O_9S_{11}$: C, 24.78; H, 4.16; S, 36.38.
Found: C, 24.66; H, 4.34; S, 35.99.

Reaction of II with thiosulfate. Two samples of II, 0.2338 g. and 0.2884 g., were shaken for twenty-four hours with 50 cc. of 0.10 *N* thiosulfate solution. A clear solution resulted. The unchanged thiosulfate was determined by the addition of excess standard iodine solution and titration of the excess iodine with thiosulfate. These titrations indicated that 1.90 and 1.91 equivalents of thiosulfate per mole of II had been consumed.

The Bunte salt was isolated and analyzed as follows. A mixture of 1.32 g. (0.005 mole) of II and 2.5 g. (0.01 mole) of sodium thiosulfate pentahydrate in 50 cc. of water was shaken for twenty-four hours. The resulting clear solution was evaporated to dryness under reduced pressure (bath temperature 40°). The residue was extracted with 50 cc. of hot ethanol and filtered. The filtrate was concentrated to 30 cc. and cooled. The white solid which separated was collected and dried over calcium chloride *in vacuo*, weight 1.15 g. (50%). The product recrystallized twice from ethanol, softened at 130° and melted at 225–230°, dec.

Anal. Calc'd for $C_8H_{16}Na_2O_7S_6$: C, 20.77; H, 3.49; Na, 9.94.
Found: C, 21.66; H, 3.67; Na, 8.95.

Preparation of II disulfoxides. A solution of 5.0 g. (0.04 mole) of 27.2% hydrogen peroxide in 25 cc. of acetic acid was cooled to 0° and added slowly to a cooled solution of 5.0 g. (0.019 mole) of II in 25 cc. of acetic acid. The resulting solution was allowed to stand overnight at room temperature. The solution was concentrated under reduced pressure to a thick sirup which was covered with 35 cc. of ether. It slowly crystallized on standing. The solid was dissolved in 50 cc. of ethanol and 150 cc. of ether and cooled overnight. The rosettes which separated were dried over calcium chloride *in vacuo*, 1.19 g., m.p. 92–96°. The filtrate was evaporated to dryness. The residue was dissolved in 10 cc. of ethanol and 50 cc. of ether was added and the solution cooled. The resulting solid was dried over calcium chloride *in vacuo*, weight 2.95 g., m.p. 75–86°. The total yield of mixed disulfoxides was 4.14 g. (74%)

The first fraction was recrystallized three times from ethanol-ether solution to yield the *α-disulfoxide* as needles, m.p. 100–101°.

Anal. Calc'd for $C_8H_{16}Cl_2O_3S_2$: C, 32.54; H, 5.46; S, 21.72; Cl, 24.02.
Found: C, 32.75; H, 5.54; S, 21.62; Cl, 24.00.

The second fraction was recrystallized three times from ethanol solution to yield the *β-disulfoxide* as long needles, m.p. 106–107°. A mixture of the two forms melted at 83–99°.

Anal. Calc'd for $C_8H_{16}Cl_2O_3S_2$. C, 32.54; H, 5.46; S, 21.72; Cl, 24.02.
Found: C, 32.76; H, 5.40; S, 21.70; Cl, 24.28.

Preparation of II disulfone. A solution of 13.6 g. (0.12 mole) of 30% hydrogen peroxide in 30 cc. of acetic acid was slowly added with cooling to 5.0 g. (0.019 mole) of II. The solution was boiled under reflux for two hours and then concentrated under diminished pressure to a thick brown sirup The sirup was dissolved in acetone and treated with Norit. Ethanol was added and the solution concentrated to 40 cc. and cooled The long white needles which separated were dried over calcium chloride *in vacuo*, m.p. 66–68°. The yield was 2.90 g. (47%). The product was recrystallized twice from ethanol-acetone solution, m.p. 70–71°.

Anal. Calc'd for $C_8H_{16}Cl_2O_5S_2$: C, 29.36; H, 4.93; S, 19.59; Cl, 21.67.
Found: C, 29.70; H, 4.87; S, 19.03; Cl, 21.30.

Solubility of II disulfone. A sample of 0.4285 g. of II disulfone was shaken with 50 g. of distilled water for forty-eight hours. The excess sulfone was collected on a tared sintered glass filter and dried over calcium chloride *in vacuo*, weight 0.2260 g. It was calculated from this value that the solubility of the sulfone was 0.405 g. per 100 g. of water. Samples of the filtrate were transferred to tared weighing bottles. The weight of solution was determined and the water allowed to evaporate in a desiccator over calcium chloride. The weighing bottles were dried to constant weight and the amount of sulfone in a given weight of water thus determined by difference. The solubility of the sulfone was determined to be 0.400 g. per 100 g. of water In another determination in which the sulfone and water were shaken together for only twelve hours, only 0.345 g. of the sulfone dissolved per 100 g. of water.

Decomposition of II disulfone in alkaline solution. A solution of the disulfone in distilled water gave no test with silver nitrate for chloride ion after forty-eight hours A little sodium bicarbonate was added to the solution. As for β-chloroethyl sulfone, a positive test for chloride ion was obtained in five minutes (1).

Preparation of α-naphthylurethan of II glycol. A mixture of 1.0 g. of II glycol and 1.5 g. of α-naphthyl isocyanate was warmed on a steam-bath. The resulting product was recrystallized from petroleum ether-ethyl acetate solution, m.p. 77–81°, weight 1.35 g The *urethan* was recrystallized four times from ethanol, m p. 84–86°.

Anal. Calc'd for $C_{30}H_{32}N_2O_5S_2$: C, 63.80; H, 5.71.
Found: C, 64.11; H, 5.93.

II-Glycol complex with silver nitrate. Since it was noted that the end point in the titration of chloride ion in hydrolyzed solutions of II was poor, standard solutions of sodium chloride and II-glycol were prepared. These solutions gave similar poor end points.

A solution of II-glycol was titrated with silver nitrate using the Mohr method. One cc. of 4% potassium chromate was added to a 5-cc. aliquot of a standard II-glycol solution. The sample was titrated with silver nitrate to an indistinct red end point. A blank was determined and it was calculated that the solution of II-glycol required 0.98 mole of silver nitrate per mole of the glycol.

A solution of 2.26 g. (0.0133 mole) of silver nitrate and 3.0 g. (0.0133 mole) of II-glycol in 10 cc. of water was prepared. The solution was concentrated under diminished pressure to a sirup. The sirup was dissolved in warm ethanol and filtered from a small amount of solid. On cooling, long heavy needles separated. The product was dried over calcium chloride *in vacuo*, m.p. 67–70°. The yield was 3.55 g. (67%). The product was recrystallized from methanol-acetone and dried over phosphoric anhydride *in vacuo*, m.p. 68–70°.

Anal. Calc'd for $C_8H_{18}O_3S_2 \cdot AgNO_3$: C, 24.25; H, 4.58; Ag, 27.23.
Found: C, 24.28; H, 4.55; Ag, 30.00.

SUMMARY

β-(β'-Chloroethylthio)ethyl ether (II), although only very slightly soluble in water, is dissolved to a considerable extent by continued shaking. Such solutions appear to contain a reactive mixture of oily sulfonium salts.

The sulfonium salt from II and two equivalents of thiodiglycol was isolated as an oil which was characterized as the Reineckate.

The two isomeric disulfoxides and the disulfone from II were prepared and characterized.

The glycol related to II, β-(β'-hydroxyethylthio)ethyl ether, forms a stable complex, m.p. 70°, with silver nitrate.

Urbana, Ill.

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

SOME REACTIONS OF 1,2-*bis*(β-CHLOROETHYLTHIO)ETHANE[1]

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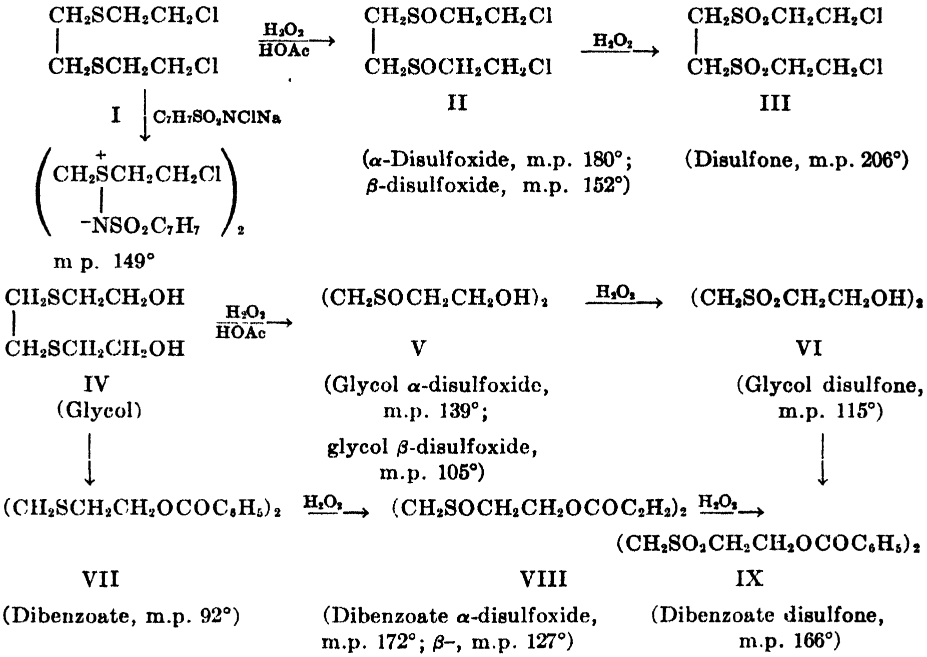
1,2-*bis*(β-Chloroethylthio)ethane (I) and the corresponding glycol, IV, were first reported by Bennett and Whincop (1). The purpose of the present investigation was to study the hydrolysis of the former and to characterize the oxidation products of both. The various transformations studied are indicated in the chart below.



$$\begin{array}{l}CH_2SCH_2CH_2Cl\\ |\\ CH_2SCH_2CH_2Cl\end{array} \xrightarrow[HOAc]{H_2O_2} \begin{array}{l}CH_2SOCH_2CH_2Cl\\ |\\ CH_2SOCH_2CH_2Cl\end{array} \xrightarrow{H_2O_2} \begin{array}{l}CH_2SO_2CH_2CH_2Cl\\ |\\ CH_2SO_2CH_2CH_2Cl\end{array}$$

I $\xrightarrow{C_7H_7SO_2NClNa}$ $\left(\begin{array}{l}CH_2\overset{+}{S}CH_2CH_2Cl\\ \quad|\\ \ ^{-}NSO_2C_7H_7\end{array}\right)_2$ m p. 149°

II (α-Disulfoxide, m.p. 180°; β-disulfoxide, m.p. 152°)

III (Disulfone, m.p. 206°)

$$\begin{array}{l}CH_2SCH_2CH_2OH\\ |\\ CH_2SCH_2CH_2OH\end{array} \xrightarrow[HOAc]{H_2O_2} (CH_2SOCH_2CH_2OH)_2 \xrightarrow{H_2O_2} (CH_2SO_2CH_2CH_2OH)_2$$

IV (Glycol)

V (Glycol α-disulfoxide, m.p. 139°; glycol β-disulfoxide, m.p. 105°)

VI (Glycol disulfone, m.p. 115°)

$$(CH_2SCH_2CH_2OCOC_6H_5)_2 \xrightarrow{H_2O_2} (CH_2SOCH_2CH_2OCOC_2H_2)_2 \xrightarrow{H_2O_2} (CH_2SO_2CH_2CH_2OCOC_6H_5)_2$$

VII (Dibenzoate, m.p. 92°)

VIII (Dibenzoate α-disulfoxide, m.p. 172°; β-, m.p. 127°)

IX (Dibenzoate disulfone, m.p. 166°)

Considerable difficulty was encountered in establishing suitable conditions for the various oxidations. For example, it was only by slow, room-temperature oxidation with hydrogen peroxide in acetic acid that it was possible to isolate crystalline sulfoxides from the glycol IV. The separation of the stereoisomeric forms of the disulfoxides was accomplished only by extensive fractional crystallization.

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[1] The work reported herein was carried out under a contract, recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the University of Illinois.

[2] Present address: University of Notre Dame, Notre Dame, Indiana.

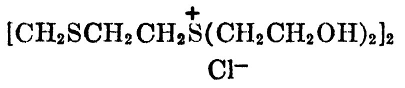
[3] Present address: University of California, Los Angeles, Calif.

The rate of hydrolysis of I in water could not be conveniently studied because of extreme insolubility. By extrapolation of the rate in aqueous dioxane solutions it has been estimated that the first-order rate constant in water at 25° should be about 0.4 min.$^{-1}$. This is four times that of β-chloroethyl sulfide, $k_{25} = 0.10$ min.$^{-1}$ [half-life at 25°, seven to eight minutes (2, 3, 4)], and about twice the value reported for β-(β′-chloroethylthio)ethyl ether (X) by Brookfield and Moelwyn-Hughes (5).

$$(ClCH_2CH_2SCH_2CH_2)_2O$$

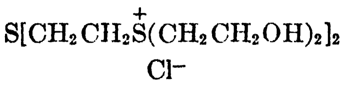
(X)

From unpublished observations of Bergmann and Fruton (6), it has been possible to estimate that the hydrolysis of the sulfonium salt XI, formed from I and two equivalents of thiodiglycol, is a first-order reaction, as is that for the corresponding salt, XII, from β-chloroethyl sulfide. The half-life for XII is about nine days, that for XI about one and one-half days. Furthermore, the half-life of the similar sulfonium salt (XIII) from X has an intermediate half-life of about 3.8 days (7).



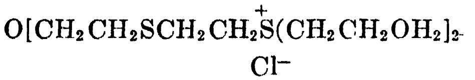
$$\underset{Cl^-}{[CH_2SCH_2CH_2\overset{+}{S}(CH_2CH_2OH)_2]_2}$$

XI



$$\underset{Cl^-}{S[CH_2CH_2\overset{+}{S}(CH_2CH_2OH)_2]_2}$$

XII



$$\underset{Cl^-}{O[CH_2CH_2SCH_2CH_2\overset{+}{S}(CH_2CH_2OH_2]_2}$$

XIII

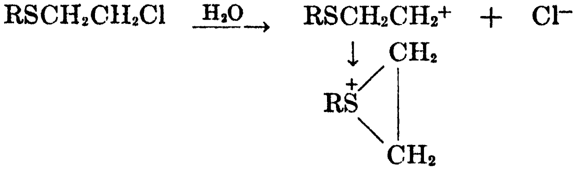
The rates thus parallel those of the corresponding chloro compounds but are about 1500 times slower.

In connection with speculation concerning the mechanism of hydrolysis of β-chloroethyl sulfides (2, 3, 4), it is of interest to compare this order of reactivity for chloro compound and sulfonium salt with examples known to proceed by S_{N_1} and by S_{N_2} mechanisms.

For example, the rate constant for the first-order (S_{N_1}) hydrolysis of dimethyl-*t*-butylsulfonium hydroxide has been determined by Gleaves, Hughes, and Ingold (8) to be 20.5 hrs.$^{-1}$ at 100°. From the data of Hughes (9) for the hydrolysis of *t*-butyl chloride in aqueous alcohol at 5 to 45°, we have estimated the first-order rate constant to be dependent on about the fifth power of the water concentration and the rate constant in pure water at 100° to be about 6×10^4 hr.$^{-1}$. The ratio of k_1 for the chloride and the sulfonium ion would thus be about 3000 in this case.

The second-order (S_{N_2}) rate constants for the reactions of ethyl chloride (10) and triethylsulfonium ion (8) with hydroxyl ion in ethanol at 100° differ by a factor of about 200, in this case favoring the sulfonium ion.

The first-order kinetics, the effect of solvent medium and the ratio of reactivity of chloride to sulfonium ion thus all seem to favor an interpretation of the hydrolytic reactions of the β-chloroethyl sulfides as true "$S_{N}1$" solvolytic reactions. This conclusion is further supported by the ease of conversion of β-thioalcohols to chlorides, which is accomplished readily and rapidly by treatment with concentrated hydrochloric acid with much the same ease as the conversion of *t*-butyl alcohol to the chloride. It thus appears that the cyclic ethylene sulfonium salt postulated as an intermediate for many reactions of β-chloroethylsulfides (4) must be the result of the stabilization of the cation so formed but that this cyclization must not be the factor supplying the principal driving force for the reactions.



EXPERIMENTAL

Approximate solubility of 1,2-bis(β-chloroethylthio)ethane[4] *(I) in water.* One gram of I was dissolved in 100 cc of absolute ethanol by shaking at room temperature. When 1 cc. of this solution was added to 100 cc. of distilled water, solid precipitated and did not redissolve The alcohol solution was then added dropwise to 100 cc. of water shaking after each drop was added, and it was found that the addition of five drops led to separation of fine solid particles which floated on the surface of the water. This indicated that the solubility was below 25 mg. per liter of water.

Reaction of 1,2-bis(β-chloroethylthio)ethane (I) with sodium thiosulfate. The method used for the determination of the rate of hydrolysis of β-chloroethyl sulfide (4) was applied with certain modifications. A 1% solution of I in purified dioxane(11) was prepared. When 1 cc. of this solution was added to 25 cc. of aqueous 0.01 *N* thiosulfate solution, fine particles of solid separated. The experiments were therefore carried out by adding at least 10 cc. of dioxane to the thiosulfate before the addition of the solution of I; no solid precipitated under these conditions. After various intervals, 25 cc. of 0.01 *N* iodine in potassium iodide solution was added and the excess iodine was titrated with thiosulfate. A blank containing only dioxane and thiosulfate was always run concurrently and the small correction applied to the analytical data. The normality of the standard solutions was checked every few hours. The results are summarized in Figs. 1 and 2 and in Tables I and II.

An extrapolation of the values for k_1 in Table II (see Fig. 3) indicates a value for k_1 in pure water of 0.4 min.^{-1} and a dependence of k_1 on approximately the fourth power of the water concentration.

Hydrolysis of 1,2-bis(β-chloroethylthio)ethane (I) determined by use of sodium thiosulfate reaction. To 25 cc. of distilled water and 10 cc. of dioxane in six flasks was added 1 cc. of the dioxane solution of I. After five, ten, fifteen, twenty-five, forty, and eighty minutes, 22.20 cc. of thiosulfate solution was added. Forty minutes after the thiosulfate was added to each flask, 25.00 cc. of iodine solution was run in and the excess iodine was back-titrated with thiosulfate. On the basis of the results of the preceding experiments it was assumed that the 1,2-*bis*(β-chloroethylthio)ethane which had not been hydrolyzed at the time the thiosulfate was added would react with it to the extent of 90% within forty minutes. The results are summarized graphically in Fig. 4.

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[4] This vesicant and toxic material was handled with great care, using rubber gloves over polyvinyl alcohol gloves.

1,2-bis(β-Chloroethylthio)ethane α- and β-disulfoxides (II). To a solution of 30 g. (0.137 mole) of I in 150 cc. of dioxane in a beaker was added 30 cc. (0.291 mole) of 30% hydrogen peroxide, and the solution was warmed on a hot plate. When the temperature reached 75°, the solution began to boil; it was removed from the hot plate but continued to boil vigorously for three or four minutes, the temperature having risen to 90°. As the solution cooled to about 80°, crystals began to form, and by the time room temperature was reached, the beaker contained a mass of white solid After cooling in ice, the white crystals were collected and dried *in vacuo* for thirty-six hours. They weighed 28 g. (81%) m.p. 147–159°.

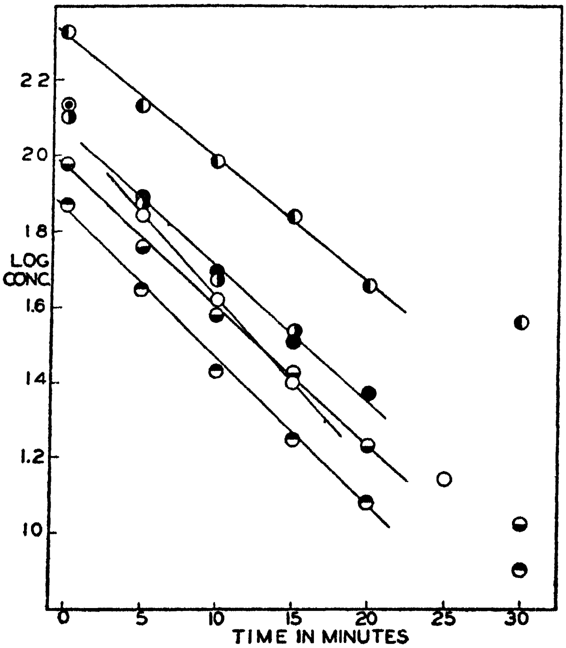

FIG. 1. Rate of Reaction of I with Thiosulfate in 32% Aqueous Dioxane

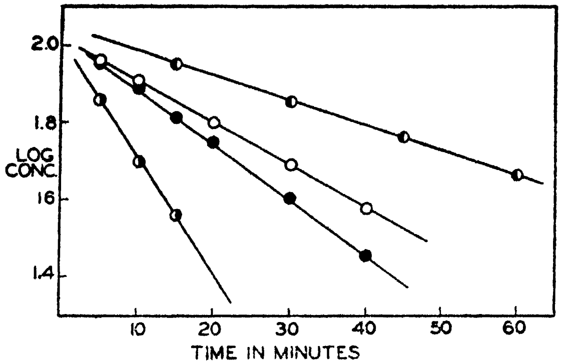

FIG. 2. Rate of Reaction of I with Thiosulfate in Aqueous Dioxane. ◑, 43.2% dioxane; ●, 48.6% dioxane; ○, 55.8% dioxane; ◐, 60.7% dioxane.

These crystals were dissolved in 130 cc. of hot glacial acetic acid. The solution was filtered hot and cooled in ice. The white crystals which separated, when dry, melted at 174–176° and amounted to about 13 g. The filtrate was evaporated to dryness under an air stream, and the 15 g. of white powdery residue had the melting point 150–156°. The higher-melting fraction was recrystallized from 1 liter of methanol; the melting point was then 175–177°. Another recrystallization from a mixture of 150 cc. of methanol and 70 cc. of glacial acetic acid gave fine shiny white crystals of α-disulfoxide melting at 176–178°. A sample of this material recrystallized from glacial acetic acid and then from methanol melted at 179–180°. The material has been referred to herein as the *α-disulfoxide.*

Anal. Calc'd for $C_6H_{12}Cl_2O_2S_2$: C, 28.69; H, 4.82; S, 25.53.
Found: C, 29.02; H, 5.08; S, 24.68.

A 12-g. sample of the lower-melting, more soluble crude β-disulfoxide above was purified by suspending it in 200 cc. of absolute ethanol and boiling under reflux for half an hour. The mixture was filtered hot to remove insoluble material, and the filtrate was cooled to 15°. The precipitate which formed in the filtrate was collected and dried *in vacuo*; 7.6 g., m.p. 151–152°. A sample of this material, referred to as *β-disulfoxide,* was recrystallized for analysis from ethanol as fine microcrystals, m.p. 151–152°.

TABLE I

REACTION OF 1,2-*bis*(β-CHLOROETHYLTHIO)ETHANE (I) WITH THIOSULFATE AT ROOM TEMPERATURE (*CA.* 28°) IN DIOXANE

$10^3 \times [I]_0$ (MOL./L.)	$10^3 \times [S_2O_3^{=}]_0$ (MOL./L.)	% DIOXANE	k_1 (MIN.$^{-1}$)
2.13	7.15	32.6	0.072
1.35	7.00	31.4	.105
1.35	7.00	31.2	.081
1.35	7.40	31.4	.087
0.95	5.05	32.0	.081
.74	3.88	32.4	.091
			0.086 ± .008

TABLE II

REACTION OF 1,2-*bis*(β-CHLOROETHYLTHIO)ETHANE (I) WITH THIOSULFATE AT ROOM TEMPERATURE IN AQUEOUS DIOXANE

$10^3 \times [I]_0$	$10^3 \times [S_2O_3^{=}]_0$	% DIOXANE	k_1 (MIN.$^{-1}$)
—	—	*ca.* 32	0.086
1.82	6.12	43.2	.071
1.07	5.54	48.6	.032
1.07	4.50	55.8	.025
1.07	4.25	60.7	.014

Anal. Calc'd for $C_6H_{12}Cl_2O_2S_2$: C, 28.69; H, 4.82.
Found: C, 28.57; H, 5.00.

The mixture of the two isomers above was found to be very slightly soluble in ether, benzene, carbon tetrachloride, acetone, and petroleum ether (b.p. 90–110°). It was more soluble in chloroform, dioxane, methanol, and ethanol and quite soluble in glacial acetic acid. The pure β-disulfoxide was found to be appreciably more soluble in methanol, ethanol, and chloroform and much more soluble in glacial acetic acid than the α-disulfoxide. The solubility of the two isomers in dioxane was about the same.

The aqueous solubility of the α-disulfoxide was found to be 0.229 g. per 100 cc. of water at 30°. The β-disulfoxide was soluble to the extent of 1.09 g. per 100 cc. of water at 30°.

1,2-bis(β-Chloroethylthio)ethane disulfone (III). **To a suspension of 0.83 g. (0.0038 mole) of the α-disulfoxide (m.p. 174–176°) in 85 cc. of dioxane was added 5 cc. (0.0049 mole)**

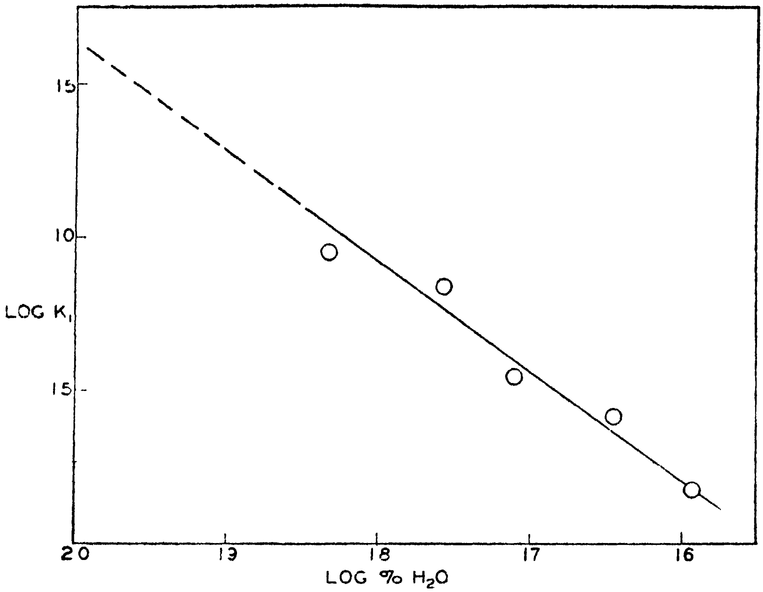

FIG. 3. Variation of the Rate Constant for the Hydrolysis of I with the Composition of the Aqueous Dioxane Solvent.

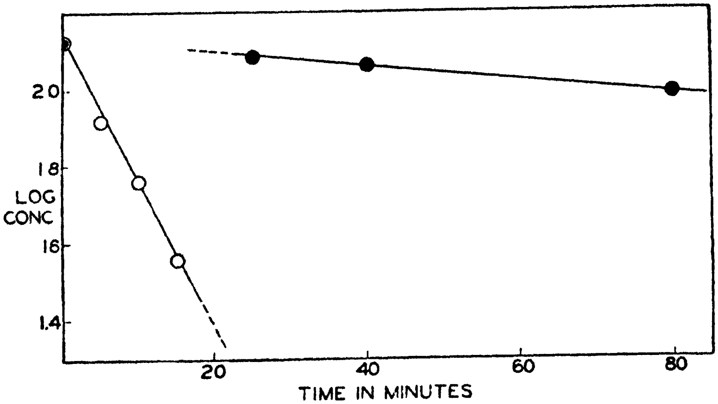

FIG. 4. Hydrolysis of I in 31.2% Aqueous Dioxane. ○, First Chlorine, k_1 = 0.085; ●, Second Chlorine, k_1 = 3 98 × 10^{-3}.

of 30% hydrogen peroxide, and the mixture was heated to gentle reflux. All the solid went into solution and the heating was continued for five hours. The cold reaction mixture was diluted with 100 cc. of water. The flocculent precipitate of white solid was collected and dried *in vacuo*. The yield was 0.75 g. of powdery solid melting at 203–205°. In like manner, the β-disulfoxide (m.p. 151–153°) was converted to disulfone, m.p. 201–203°. After two recrystallizations from methanol-acetic acid, it melted at 205–206° (6).

Anal. Calc'd for $C_6H_{12}Cl_2O_4S_2$: C, 25.45; H, 4.27; S, 22.64.
Found: C, 25.46; H, 4.47; S, 22.84.

A mixture of the α- and β-disulfoxides (7.8 g., 0.031 mole) was dissolved in 50 cc. of hot glacial acetic acid and treated with 12 cc. (0.12 mole) of 30% hydrogen peroxide. The solution was heated to gentle reflux. After fifteen minutes a voluminous white precipitate appeared. The heating was maintained for an hour with occasional shaking and the mixture was allowed to cool overnight. It was then filtered and the solid was washed with 200 cc. of water and dried in a vacuum desiccator. The yield was 8.03 g. (91.5%) of white powder melting at 204–206°.

1,2-*bis*(β-Chloroethylthio)ethane was similarly oxidized with hydrogen peroxide in acetic acid to form the disulfone in 84% yield directly.

The aqueous solubility of the disulfone was only 0.008 g. per 100 cc. of water at 30°.

Stability of the disulfoxides (II) and disulfone (III) toward hydrolysis. A 0.1-g. sample of the α-disulfoxide was dissolved in 100 cc. of distilled water in a 250 cc. volumetric flask and more distilled water was added to the mark. A solution of β-disulfoxide was prepared in the same way. In 140 cc. of distilled water was placed 0.1 g. of the disulfone. The mixture was shaken for forty-eight hours and then the undissolved disulfone was collected on a filter. The filtrate was poured into a 250-cc. volumetric flask, and more distilled water was added to the mark. These solutions were allowed to stand in the glass-stoppered flasks for a month. At intervals during this time each solution was tested for chloride ion by adding a few cubic centimeters to a 5% silver nitrate solution. No precipitate was ever obtained.

After the solutions had stood for a week, 95 cc. of the disulfone solution was poured into a 125-cc. Erlenmeyer flask and 5 g. of sodium bicarbonate was added. The mixture was stirred until all the bicarbonate dissolved. This solution was then stoppered and allowed to stand for twenty-five days. It was frequently tested for chloride ion by acidifying a 5-cc. sample with nitric acid and adding silver nitrate solution. No precipitate was ever obtained.

Reaction of chloramine-T with 1,2-bis(β-chloroethylthio)ethane (I) in dioxane. Two grams of I was dissolved in 10 cc. of dioxane and 40 cc. of a 12.5% chloramine-T solution was added. An oily solid precipitated immediately. The oily solid was washed repeatedly with 30-cc. portions of methanol. Less than a gram of the resulting white powder was recrystallized from 650 cc. of methanol to yield fine, lustrous crystals which melted at 147.5–149°. A sample was prepared for analysis by recrystallizing a small amount of these crystals from 35 cc. of methanol. The melting point of this sample was 148–149°, and the composition found corresponded to the *disulfilimine* derivative of I.

Anal. Calc'd for $C_{20}H_{26}Cl_2N_2O_4S_4$: C, 43.08; H, 4.70.
Found: C, 43.31; H, 4.67.

Treatment of 1,2-bis(β-hydroxyethylthio)ethane (IV) in acetic acid with hydrogen peroxide. To a solution of 10 g. (0.055 mole) of the glycol IV in 50 cc. of glacial acetic acid was added with cooling 13 cc. (0.113 mole) of 27% hydrogen peroxide. The solution was allowed to stand at room temperature for forty-eight hours and then the solvents and excess hydrogen peroxide were removed by distillation under diminished pressure (25 mm.). The water-bath beneath the distillation flask was not heated above 50°. The residue, which crystallized upon standing, was taken up in 50 cc. of hot absolute ethanol, placed in a stoppered flask, and allowed to cool to room temperature overnight. Fine crystals separated, 5.5 g., m.p. 85–132°. The filtrate from these crystals deposited more solid on standing, so it was cooled to 0°, and the second crop was collected, 1.3 g. of white powder melting at 98–111°, with sintering at 85°. Neither of these crops of crystals was hygroscopic.

After extensive fractional crystallization from ethanol, samples of glycol α-disulfoxide, melting at 137–139°, and of glycol β-disulfoxide, melting at 102.5–105°, were obtained.

Anal. Calc'd for $C_6H_{14}O_4S_2$: C, 33.63; H, 6.58.
Found: (α-isomer): C, 33.94; H, 6.74.
(β-isomer): C, 33.71; H, 6.73.

When a few crystals of mixed glycol disulfoxides (V) were added to a few cubic centimeters of concentrated hydriodic acid, a distinct reaction took place, as shown by the intense coloration of the solution by free iodine and by the heat which was produced. No precipitation of solid or oily drops occurred when the solution was diluted with water, and it was presumed that the reaction which took place was the reduction of the disulfoxide to the glycol IV.

1,2-bis(β-Hydroxyethylsulfonyl)ethane (VI). To a solution of 20 g. (0.110 mole) of the glycol IV in 100 cc. of glacial acetic acid was added portionwise with cooling 75 cc. (0.652 mole) of 27% hydrogen peroxide. The stoppered flask was allowed to stand for eighty-four hours and the solvents were removed by distillation at 25 mm. The residue was taken up in 100 cc. of hot absolute ethanol which was filtered and cooled, to give crystals melting at 87–105°. Recrystallization from dioxane raised the melting point to 96–113°, 15 g. This product was treated with 10 cc. of glacial acetic acid and 10 cc. of cold ether, and the mixture was stirred thoroughly while being cooled in an ice-bath. The crystals were washed repeatedly with cold ether and then dried *in vacuo*. The melting point after this treatment was 108–113°, and recrystallization from dioxane brought it to 112–114°, sintering slightly from 102°.

A small sample was recrystallized from pure dry dioxane yielding crystals which melted at 112–114°, sintering from 108°. A second recrystallization from the same solvent raised the melting point of the glycol disulfone (VI) to 113.5–114.5°, sintering slightly at 110°.

Anal. Calc'd for $C_6H_{14}O_6S_2$: C, 29.26; H, 5.73.
Found: C, 29.39; H, 5. 70.

In contrast to the glycol disulfoxides, which gave an intense color with hydriodic acid, the glycol disulfone gave only a very pale color.

One gram of the crude disulfone was dissolved in water and treated with benzoyl chloride by the Schotten-Baumann method. The ester was recrystallized from absolute ethanol, m.p. 163–164°, sintering from 156°. It was identical with the dibenzoate disulfone (IX) prepared as described below.

Oxidation of 1,2-bis(β-benzoxyethylthio)ethane and separation of the two dibenzoate disulfoxides produced. Fifteen grams (0.08 mole) of the glycol IV was dissolved in 30 cc. of anhydrous pyridine and 18 cc. (0.16 mole) of benzyol chloride was added. The solution was cooled until the initial reaction subsided, then warmed one or two minutes on the hot plate and poured, with stirring, into 100 cc. of water. After cooling, the precipitate was collected, then removed to a beaker and washed with 50 cc. of 5% sodium carbonate. The wash solution was removed, and the precipitate was washed on the filter with another 10 to 15 cc. of the same solution. The product was then recrystallized three times from ethanol, using Darco treatment the last time, and 15.7 g. (50.4%) of nearly white crystalline ester melting at 90–92° was obtained.

Anal. Calc'd for $C_{20}H_{22}O_4S_2$: C, 61.51; H, 5.68.
Found: C, 61.33; H, 5.85.

Ten grams (0.026 mole) of this product was dissolved in 100 cc. of glacial acetic acid by warming and cooled to room temperature without separation of the solute. To this solution was added with cooling 6 cc. (0.052 mole) of 27% hydrogen peroxide, and the solution was allowed to stand for forty-eight hours. The solvents were then removed by distillation under diminished pressure (25 mm.), and the solid residue was taken up in boiling ethanol, about 500 cc. being required to dissolve it completely. The alcohol solution was filtered hot and then cooled, giving 8.8 g. of crystals which melted at 128–165°. The filtrate from these crystals was evaporated until only 5 cc. of liquid remained, which smelled strongly of acetic acid. This was diluted with water, and the precipitated solid was collected. Recrystallization from 20 cc. of ethanol gave needles melting at 125.5–127°. Five grams of the mixture melting at 128–165° was fractionated by recrystallizations from ethanol-acetic acid and ethanol. A yield of 2.25 g. of crystals melting at 168–170°, sintering from 160° and 1.9 g. of crystals melting at 126–128° was obtained.

The higher-melting material, dibenzoate α-disulfoxide (VIII), was recrystallized for analysis from ethanol, m.p. 171–172°. Part of the crystals melting at 126–128° were recrystallized for analysis from 20 cc. of ethanol and then melted at 126–127° (β-isomer).

Anal. Calc'd for $C_{20}H_{22}O_6S_2$: C, 56.85; H, 5.25.
Found: (α-isomer); C, 57.04; H, 5.39.
(β-isomer); C, 56.67; H, 5.28.

Oxidation of dibenzoate α- and β-disulfoxides to the same disulfone. One-half-gram (0.0012 mole) samples of the two disulfoxides above were dissolved in 10-cc. portions of glacial acetic acid and 4 cc. (0.035 mole) of 27% hydrogen peroxide was added to each. No heat was evolved, so the solutions were heated to boiling for a few seconds and then allowed to cool. Within thirty minutes, long, slender needles had separated from solution in both flasks. After standing overnight these crystals were collected, washed with ether, and dried *in vacuo*. The melting point of both products was 165–166° and the mixed melting point was the same. The melting point of a mixture of the product from the dibenzoate α-disulfoxide with the starting material was 150–157°, sintering from 140°.

The product from the dibenzoate β-disulfoxide was recrystallized from glacial acetic acid, but the melting point was lowered to 163–165°, with sintering from 150°. Therefore, a procedure to avoid the possibility of transesterification was used. The ester was dissolved in hot dioxane, filtered through sintered glass, and reprecipitated by adding cold ether through the sintered filter. This gave material melting at 164–165°, sintering at 161°.

Anal. Calc'd for $C_{20}H_{22}O_8S_2$: C, 52.85; H, 4.88.
Found: C, 53.15; H, 5.07.

SUMMARY

The two sulfoxides and the sulfone from oxidation of 1,2-*bis*(β-chloroethylthio)ethane, the corresponding glycol and its dibenzoate have been prepared and characterized.

From the rate of hydrolysis of the chloro compound in aqueous dioxane, it has been estimated that it hydrolyzes about four times as rapidly as β-chloroethyl sulfide.

A comparison of the rates of hydrolysis of three β-chloroethyl sulfides with the corresponding sulfonium salts indicates a remarkable resemblance to processes of the "S_N1" rather than the "S_N2" type.

URBANA, ILL.

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

SOME TERTIARY DIAMINES DERIVED FROM 1,2-*bis*(β-CHLOROETHYLTHIO)ETHANE[1]

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In view of the reported activity of several long-chain diamines against certain tropical diseases (1), it seemed of interest to ascertain whether analogs, in which pairs of carbons had been replaced by sulfur atoms, might have similar activity. In particular, since the glycol I, 1,2-*bis*(β-hydroxyethylthio)ethane, is readily available, its conversion to a number of simple diamines has been investigated.

The corresponding chloro compound, II, was remarkably inert toward secondary amines in ether, petroleum ether or dioxane. It condensed with diethylamine in boiling ethanol (2) but dibutylamine failed to react under these conditions. The condensation of the latter amine, as well as piperidine and *n*-propylaniline was accomplished satisfactorily in boiling 90% dioxane as solvent.

The sulfone IV (3) was much more reactive, condensing readily with diethylamine or piperidine with the evolution of considerable heat to yield the diamino disulfones (VII).

Attempts to convert three of the diamines III into disulfones by oxidation with hydrogen peroxide in acetic acid led to cleavage of the molecule. From the diethylamino and piperidyl compounds, the product isolated was the diamino sulfone V. From the dibutylamino compound, the product isolated after treatment with hydrochloric acid analyzed correctly for β-di-*n*-butylaminoethanesulfonic acid (VI).

$$\begin{tikzcd}
\underset{\text{I}}{(HOCH_2CH_2SCH_2)_2} \arrow[r, "SOCl_2"] & \underset{\text{II}}{(ClCH_2CH_2SCH_2)_2} \arrow[r, "H_2O_2", "HOAc"'] \arrow[d, "R_2NH"'] & \underset{\text{IV}}{(ClCH_2CH_2SO_2CH_2)_2} \arrow[d, "R_2NH"'] \\
\underset{\text{V}}{(R_2NCH_2CH_2)_2SO_2} & \underset{\text{III}}{(R_2NCH_2CH_2SCH_2)_2} \arrow[l, "H_2O_2", "HOAc"'] & \underset{\text{VII}}{(R_2NCH_2CH_2SO_2CH_2)_2} \\
+ & & \\
\underset{\text{VI}}{R_2NCH_2CH_2SO_2OH} & &
\end{tikzcd}$$

A somewhat similar cleavage of a dithioethane on oxidation with hydrogen peroxide in acetic acid has been previously observed (4). It seems likely that the course for the reaction may involve a reversible dissociation of the disulfone to a vinyl sulfone (VIII) and a sulfinic acid (IX) (5). The dissociation is then driven to completion by oxidation of the sulfinic acid.

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[1] The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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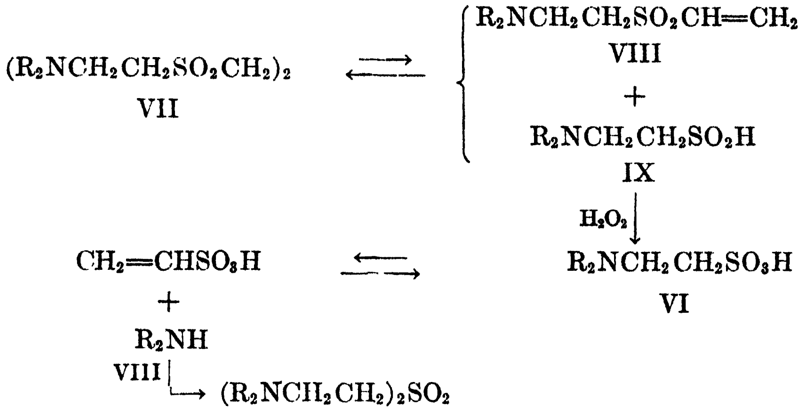

$$(R_2NCH_2CH_2SO_2CH_2)_2 \text{ (VII)} \rightleftarrows \left\{ \begin{array}{c} R_2NCH_2CH_2SO_2CH{=}CH_2 \\ \text{VIII} \\ + \\ R_2NCH_2CH_2SO_2H \\ \text{IX} \end{array} \right.$$

$$\text{IX} \xrightarrow{H_2O_2} R_2NCH_2CH_2SO_3H \text{ (VI)}$$

$$CH_2{=}CHSO_3H + R_2NH \rightleftarrows R_2NCH_2CH_2SO_3H \text{ (VI)}$$

$$R_2NH \xrightarrow{\text{VIII}} (R_2NCH_2CH_2)_2SO_2$$

The diamines derived from II and two related disulfones were submitted for assay against avian malaria. The diethyl (SN-6715)[4] and phenyl propyl (SN-8788) diamines (III) showed activity about one-tenth that of quinine.

EXPERIMENTAL[5]

1,2-bis(β-Chloroethylthio)ethane (II)[6] was prepared by addition over a period of one and one-half hours of 48 cc. (0.67 mole) of thionyl chloride in 192 cc. of dry ether to 60 g. (0.33 mole) of the glycol (I) in 300 cc. of cold dry ether. After an additional half-hour of stirring, eight or ten g. of decolorizing charcoal was added, the mixture was stirred fifteen minutes while boiling to reflux and was filtered. After evaporation to about 100 cc., cooling in an ice-salt bath precipitated 52 g. (72%) of white crystalline product, m.p. 46–50° [lit. (6), 54°].

1,2-bis(β-Diethylaminoethylthio)ethane dihydrochloride (SN-6715). Fifty grams (0.275 mole) of glycol I was converted to the chloro compound II as described above. In order to avoid handling this toxic and vesicant material, the ether and excess thionyl chloride were removed by distillation and 50 cc. of absolute ethanol, 35 g. (0.33 mole) of sodium carbonate and 65 cc. (0.63 mole) of diethylamine were added to the residue. The mixture was heated to reflux and stirred overnight. The hot solution was decanted from the sodium chloride and this residue was boiled with two portions of ethanol which were decanted and added to the rest of the solution. The alcohol was removed by distillation. To the residue (two layers) was added 185 cc. of 10% hydrochloric acid and the acid solution was extracted with three 50-cc. portions of ether to remove any unchanged sulfide. Pellet potassium hydroxide was added to the acid layer until it was distinctly basic. The oil which separated was extracted with ether and the ether solution was dried with magnesium sulfate. Dry hydrogen chloride was bubbled rapidly into the ether solution, and the oil which began to precipitate quickly solidified to a white solid, 47.3 g., m.p. 174–176°. Recrystallization from 250 cc. of absolute ethanol yielded 21.1 g. (21%), m.p. 184.5–185.5°.

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[4] The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds will be tabulated in a forthcoming monograph.

[5] Analyses by Miss Theta Spoor. All melting points uncorrected.

[6] This toxic and vesicant material was handled with great care using rubber gloves over polyvinyl alcohol gloves.

Anal. Calc'd for $C_{14}H_{34}Cl_2N_2S_2$: C, 46.01; H, 9.38; Cl^-, 19.4.
Found: C, 46.15; H, 9.51; Cl^-(Volhard), 19.5.

1,2-bis(β-Di-n-butylaminoethylthio)ethane dihydrobromide (SN-7286). To 30 g. (0.14 mole) of II in 240 cc. of 90% dioxane was added 155 cc. (0.92 mole) of di-*n*-butylamine. The solution was boiled under reflux for five hours. The dioxane and most of the excess secondary amine were removed by distillation under diminished pressure. To the residue was added 200 cc. of 10% sodium hydroxide and the mixed amines were extracted with four or five portions of ether. Most of the unreacted di-*n*-butylamine was removed by distillation and the residue was treated with 200 cc. of 10% sodium hydroxide and 25 cc. of benzenesulfonyl chloride. The mixture was shaken for several minutes in a stoppered flask and then ether and 150 cc. of 18% hydrochloric acid was added. The acid extract was made basic with sodium hydroxide pellets and the product was extracted with ether and the combined extracts dried over magnesium sulfate. Hydrogen bromide was bubbled through the mixture, and the salt precipitated as an oil which began to crystallize almost immediately. After standing overnight, the ether was decanted from the precipitate and replaced with enough hot ethyl acetate containing a little absolute ethanol to dissolve the salt. Darco was added and the mixture was boiled and filtered. From the filtrate was obtained 19.5 g. (25%) of fine white crystals, m.p. 110–112°. A sample was prepared for analysis by another recrystallization from ethyl acetate, m.p. 111–112.5°.

Anal. Calc'd for $C_{22}H_{50}Br_2N_2S_2$: C, 46.63; H, 8.90.
Found: C, 46.52; H, 9.01.

A *picrate* of the product was prepared by adding about 5 cc. of the ether solution to an equal volume of a saturated solution of picric acid in dry ether. The compound precipitated as an oil but was induced to crystallize by scratching with a glass rod. After three recrystallizations from absolute ethanol, the picrate melted at 117–119° (mixed melting point with picric acid, 80–119°)

Anal. Calc'd for $C_{34}H_{54}N_8O_{14}S_2$: C, 47.29; H, 6.30.
Found: C, 47.23; H, 6.37.

1,2-bis(β-Piperidylethylthio)ethane dihydrochloride (SN-7285) was prepared in a similar fashion. Recrystallization from ethanol afforded a 60% yield of small white needles, m.p. 266–268° (dec.).

Anal. Calc'd for $C_{16}H_{34}Cl_2N_2S_2$: C, 49 34; H, 8.80.
Found: C, 49.71; H, 8.87.

1,2-bis(β-n-Propylphenylaminoethylthio)ethane dihydrochloride (SN-8788) was prepared in a similar fashion, except that the reaction of *n*-propylaniline and II in boiling 90% dioxane required at least twenty-four hours. The product, purified by crystallization from alcohol and ether, was obtained in 35% yield, m.p. 190–191°.

Anal. Calc'd for $C_{24}H_{38}Cl_2N_2S_2$: C, 58.87; H, 7.82.
Found: C, 59.01; H, 8.02.

Treatment of 1,2-bis(β-diethylaminoethylthio)ethane dihydrochloride with hydrogen peroxide in acetic acid. To 4.4 g. (0.012 mole) of the diamine salt was added 20 cc. of glacial acetic acid and 10 cc. (0.097 mole) of 30% hydrogen peroxide. The solution was boiled under reflux for seventeen hours, the brown reaction solution was diluted with water and pellet sodium hydroxide was added until the solution was distinctly basic. A flocculent semi-solid precipitate separated and was extracted with three or four portions of ether. The ether was dried over magnesium sulfate and then evaporated under an air stream. A small amount of brown oil remained which did not crystallize on standing a few hours. The oil was redissolved in dry ether and the solution was treated with hydrogen chloride. The amine salt precipitated as an oil but quickly crystallized. The ether was decanted and the crude salt was recrystallized from ethyl acetate after treatment with Darco: a powdery almost-white product was obtained which melted with decomposition at 201–202°. Two recrystallizations from ethyl acetate-ethanol mixtures gave a product which melted at 199–200°. Half of this product was prepared for analysis by recrystallization from absolute ethanol; the melting point was then 197–197.5°. The analysis did not agree with the composition of the expected diamino disulfone (VII).

The neutral equivalent found and the analysis correspond very well to the structure of the known diethylamino derivative of β-chloroethyl sulfone (V), m.p. 202–202.5°, corr. (2).

Anal. Calc'd for $C_{14}H_{34}Cl_2N_2O_4S_2$: C, 39.15; H, 7.98; N.E., 215.
Calc'd for $C_{12}H_{30}Cl_2N_2O_2S$: C, 42.72; H, 8.96; N.E., 169.
Found: C, 42.90; H, 9.18; N.E., 169±3.

Treatment of 1,2-bis(β-N-piperidinoethylthio)ethane dihydrochloride with hydrogen peroxide in acetic acid. A solution of 3 g. (0.008 mole) of the diamine salt in 20 cc. of glacial acetic acid and 10 cc. (0.097 mole) of 30% hydrogen peroxide was boiled under reflux for five hours. The reaction mixture was diluted with water, neutralized with pellet sodium hydroxide and extracted with ether. The solid which separated between layers was collected, dissolved in about 100 cc. of water, and then extracted with ether, combining the ether layers with the main extracts. The ether was dried over magnesium sulfate and then saturated with hydrogen chloride. The oil which precipitated crystallized on standing. It was recrystallized from absolute ethanol-ethyl acetate, and a light tan powder was obtained which darkened at 210–215° and decomposed at 220° to a black liquid. After three recrystallizations from absolute ethanol, the product melted at 211–214°, sintering from 200°. A sample was prepared for analysis by recrystallization from 20 cc. of absolute ethanol and was dried at 100° (2 mm.) for four hours. Most of the sample melted at 206°, but it did not completely liquefy until the temperature was 260°. The analysis was not correct for the expected diamino disulfone (VII), but checked fairly well for the corresponding β-aminoethyl sulfone derivative (V).

Anal. Calc'd for $C_{16}H_{34}Cl_2N_2O_4S_2$: C, 42.37; H, 7.56.
Calc'd for $C_{14}H_{30}Cl_2N_2O_2S$: C, 46.53; H, 8.37.
Found: C, 46.67; H, 8.79.

Treatment of 1,2-bis(β-di-n-butylaminoethylthio)ethane dihydrobromide with hydrogen peroxide in acetic acid. A solution of 3 g. (0.005 mole) of the diamine salt in 20 cc. of glacial acetic and 10 cc. (0.097 mole) of 30% hydrogen peroxide was boiled under reflux five hours. The reaction mixture was diluted with water and neutralized with pellet sodium hydroxide. The flocculent precipitate was extracted with ether, but some of the material was not soluble in either water or ether. The combined ether layers were dried over magnesium sulfate and saturated with hydrogen chloride. The oily precipitate was recrystallized twice from absolute ethanol-ethyl acetate; the small amount of product obtained decomposed at 264° to a black liquid. The sample was prepared for analysis and the melting point of the fine crystals was the same after drying overnight at 100° (2 mm.). The composition found did not correspond to either the expected disulfone (VII) or the β-aminoethyl sulfone derivative (V) but agreed fairly satisfactorily for the hydrochloride of β-di-*n*-butylaminoethanesulfonic acid (VI).

Anal. Calc'd for $C_{22}H_{50}Cl_2N_2O_4S_2$: C, 48.78; H, 9.30.
Calc'd for $C_{20}H_{46}Cl_2N_2O_2S$: C, 53.35; H, 10.31.
Calc'd for $C_{10}H_{24}ClNO_3S$: C, 43.85; H, 8.87.
Found: C, 43.31, 43.03; H, 9.25, 9.08.

Preparation of 1,2-bis(β-diethylaminoethylsulfonyl)ethane dihydrochloride (VII, SN-8786). To 30 g. (0.106 mole) of disulfone IV in 250 cc. of dioxane, 50 cc. (0.49 mole) of diethylamine was added dropwise within about five minutes. The temperature of the mixture rose nearly to the boiling point, and the stirred mixture was heated to reflux for one hour. After standing thirty-six hours at room temperature, the mixture was filtered and 22 g. (0.20 mole) of diethylamine hydrochloride (m.p. 222–223°) was collected. The filtrate and washings were combined and the dioxane and excess diethylamine were removed by distillation at reduced pressure. To the red-brown residue was added 150 cc. of 10% sodium hydroxide and the mixture was extracted with four 100-cc. portions of ether. The ether was washed with 50 cc. of water and then dried over magnesium sulfate. A solution of 22 g. of hydrogen chloride in 500 cc. of absolute ethanol was prepared and heated to boiling. The ether solution of the amine was added with stirring to this hot solution. The salt separated on cooling and, after the solution was cooled in the ice-bath, 20 g. (44%) of fine, white crystals, m.p. 184–185°, was obtained.

Anal. Calc'd for $C_{14}H_{30}Cl_2N_2O_4S_2$: C, 39.15; H, 7.98.
Found: C, 39.49; H, 8.12.

1,2-bis(β-N-Piperidylethanesulfonyl)ethane dihydrochloride was prepared from 11 g. (0.039 mole) of disulfone IV in 100 cc. of dioxane to which 20 cc. (0.20 mole) of piperidine was added. The mixture was boiled vigorously under reflux for two hours. The reaction mixture was cooled in an ice-bath until the dioxane crystallized, allowed to warm up enough to melt the dioxane and filtered. The filter cake was sucked almost dry, removed to a beaker and 50 cc. of cold water was added. The mixture was stirred well, filtered, and the crystals which were collected were washed with two or three portions of cold water. When dry, these crystals weighed 8.3 g. and melted at 145–146°. The dioxane filtrate from the first crystals was diluted with 300 cc. of distilled water and cooled in an ice-bath. When the mixture was filtered, an additional 3.2 g. of product, m.p. 140–141°, sintering from 136°, was obtained, making the total yield 11.5 g. (78%). A small sample of the first crop was prepared for analysis by recrystallization from 50% ethanol and the analysis was correct for the composition of 1,2-*bis*(β-N-piperidinoethylsulfonyl)ethane.

Anal. Calc'd for $C_{16}H_{32}N_2O_4S_2$: C, 50.49; H, 8.48.
Found: C, 5057; H, 8.28.

SUMMARY

1,2-*bis*(β-Chloroethylthio)ethane has been converted into several tertiary diamines.

Oxidation of these diamines led to cleavage to a β-dialkylaminoethyl sulfone and, apparently, a β-dialkylaminoethanesulfonic acid.

The disulfonyl diamines were successfully prepared by reaction of 1,2-*bis*(β-chloroethanesulfonyl)ethane with secondary amines.

URBANA, ILL.

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(1) British Patent No. 433,086 (1935).
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(3) PRICE AND ROBERTS, *J. Org. Chem.*, **12**, preceding paper.
(4) SNYDER, HOWE, CANNON, AND NYMAN, *J. Am. Chem. Soc.*, **65**, 2211 (1943).
(5) See KRETOW, *J. Russ. phys.-chem. Soc.*, **62**, 1 (1930) and ALEXANDER AND MCCOMBIE, *J. Chem. Soc.*, 1913, (1931) for examples of the ease of addition to vinyl sulfones.
(6) BENNETT AND WHINCOP, *J. Chem. Soc.*, **119**, 1860 (1921).

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

SOME SULFONAMIDE DERIVATIVES OF 2-AMINOBENZIMIDAZOLE[1]

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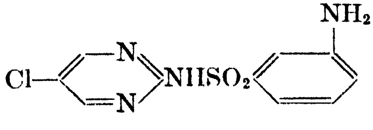
In view of the antimalarial activity of "metachloridine", 5-chloro-2-metanilamidopyrimidine, I, it seemed of some interest to prepare analogous compounds in the benzimidazole series, in particular, 2-metanilamidobenzimidazole (II) and its 5-chloro derivative (III).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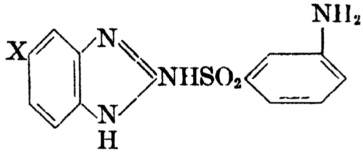
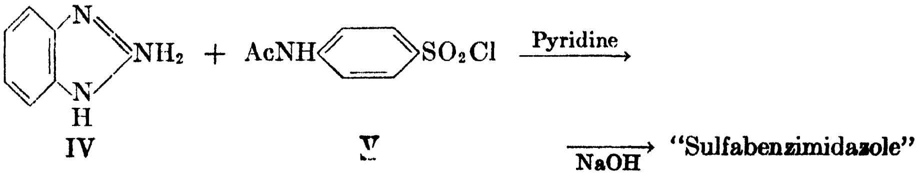
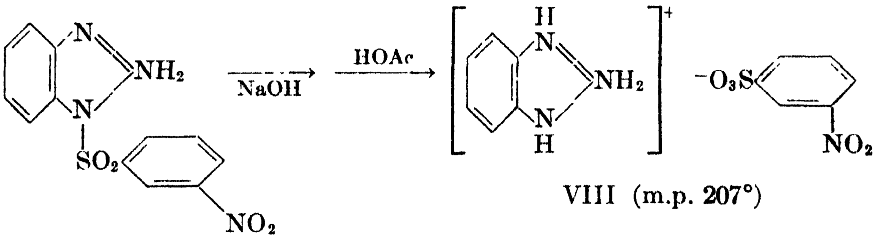

II (X = H)
III (X = Cl)

The obvious method of preparation, the coupling of 2-aminobenzimidazole with the requisite sulfonyl chloride, has been reported by Raiziss, Clemence, and Freifelder (1) to be successful for the preparation of 2-sulfabenzimidazole.


IV V "Sulfabenzimidazole" VI (m.p. 212°)

The only analysis reported by these authors, that for nitrogen, was 0.51% low and on the basis of results to be reported herein, it appears highly likely that this material (VI) was actually 2-aminobenzimidazole sulfanilate. For example, we found the substance obtained from IV and *m*-nitrobenzenesulfonyl chloride to be insoluble in cold alkali and therefore not the desired 2- but rather the 1-sulfonamide derivative (VII).


VII (m.p. 234°) VIII (m.p. 207°)

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[1] The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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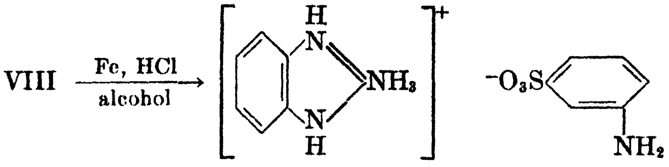
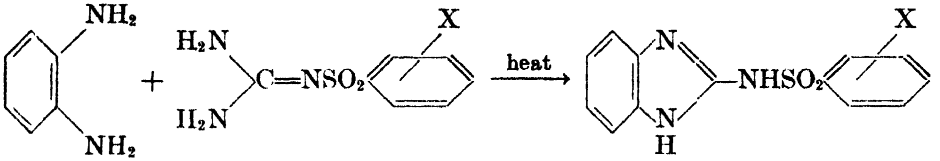
Warming with alkali, followed by acidification with acetic acid, precipitated a crystalline solid which proved to be 2-aminobenzimidazole *m*-nitrobenzenesulfonate (VIII). VIII was reduced by iron in alcoholic hydrochloric acid to yield the corresponding metanilate, IX.



IX (m.p. 180°)

The salt structure for these compounds was indicated by analysis and verified by the immediate precipitation of 2-aminobenzimidazole picrate on addition of sodium picrate to aqueous solutions.

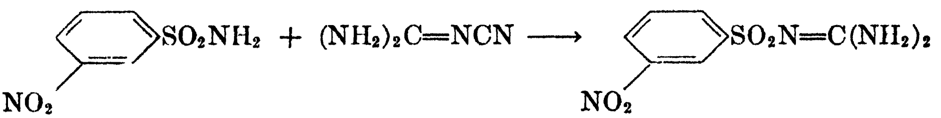
Experiment demonstrated that it was possible to prepare the desired 2-sulfonamidobenzimidazoles by heating *o*-phenylenediamine with sulfonamidoguanidines.



X (X = H, m.p. 356°)
XI (X = *m*-NO_2, m.p. 301°)
XII (X = *p*-NH_2, m.p. 322°)

XI was converted to the corresponding *m*-amino derivative, which melted above 325°.

The preparation of *m*-nitrobenzenesulfonylguanidine was accomplished by the reaction of *m*-nitrobenzenesulfonamide with dicyandiamide similar to a reaction used for the *p*-amino and *p*-acetaminobenzenesulfonylguanidines (2).



XIII (m.p. 198°)

The usual procedure involving treatment of aqueous alkaline guanidine solutions with the sulfonyl chloride produced only the *m*-nitrobenzenesulfonate salt of guanidine (m.p. 189°).[4]

Since a 2-aminoquinazoline would be more closely analagous to "metachloridine" than a 2-aminobenzimidazole, some preliminary experiments were carried out toward this end. Since Dewar (4) has shown that 2-aminoquinazoline reacts with sulfonyl chlorides at a ring nitrogen, this approach was not considered. A few experiments indicated that ethyl *p*-chloroanthranilate (XIV) reacted with benzenesulfonylguanidine to form the quinazoline.

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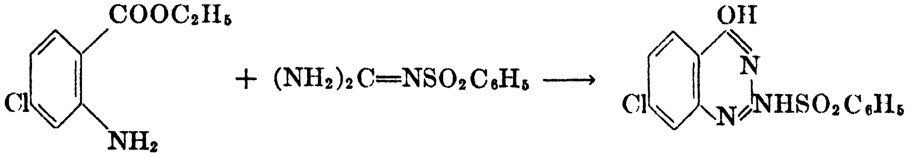
[4] We are indebted to Dr. J. M. Sprague, who pointed out to us that the material, prepared in the usual manner and reported by us to be *p*-nitrobenzenesulfonylguanidine (3), is actually the *p*-nitrobenzenesulfonate salt of guanidine. See also Karrer and Epprecht, *Helv. Chim. Acta*, **24**, 310 (1941).



XIV

XV (m.p. 286°)

Since no obvious method for satisfactory replacement of the hydroxyl in this material by hydrogen is available, a similar condensation was attempted utilizing *o*-aminobenzaldehyde and benzene or *m*-nitrobenzenesulfonylguanidine but no reaction was observed. Attempts to condense the sodium salt of benzene- or *m*-nitrobenzene-sulfonamide with 2-chloroquinazoline were also unsuccessful.

EXPERIMENTAL[5]

1-(m-Nitrobenzenesulfonyl)-2-aminobenzimidazole. To 26.6 g. (0.2 mole) of 2-aminobenzimidazole (Eastman) dissolved in 75 cc. of pyridine was added 45.0 g. (0.2 mole) of *m*-nitrobenzenesulfonyl chloride. The mixture was cooled in an ice-bath during the addition and a solid began to appear after a short time. The reaction mixture was shaken for six hours and allowed to stand overnight.

The contents of the flask were added to 600 cc. of water and the light yellow solid was isolated by filtration. A sample of this material, which was insoluble in cold sodium hydroxide, was recrystallized from ethanol. The white product, 1-(*m*-nitrobenzenesulfonyl)-2-aminobenzimidazole, melted at 233–234°.

Anal. Calc'd for $C_{13}H_{10}N_4O_4S$: C, 49.05; H, 3.17.
Found: C, 49.04; H, 3.31.

2-Aminobenzimidazole m-nitrobenzenesulfonate.[6] The crude material above was boiled with 300 cc. of 1 *N* sodium hydroxide for thirty minutes to effect complete solution. A small amount of insoluble material was removed from the hot solution and the dark red filtrate was neutralized with acetic acid and cooled. The brown solid obtained by filtration of the cold solution was dissolved in 300 cc. of water, treated three times with Darco, cooled, and filtered. After drying, 43.6 g. (65%) of the salt was obtained as light yellow sparkling needles, m.p. 204–206°. Further recrystallizations from water produced white crystals of 2-aminobenzimidazole *m*-nitrobenzenesulfonate; m.p. 206–207°.

Anal. Calc'd for $C_{13}H_{12}N_4O_5S$: C, 46.43; H, 3.60.
Found: C, 46.63, 46.61; H, 3.67, 3.73.

2-Aminobenzimidazole m-aminobenzenesulfonate. Twenty-five grams of 2-aminobenzimidazole *m*-nitrobenzenesulfonate was boiled under reflux for five hours with 80 g. of iron dust in 250 cc. of ethanol and 30 cc. of 3 *N* hydrochloric acid. The hot solution was filtered and the solvent was removed *in vacuo*. The residue was dissolved in 150 cc. of water and the solution was treated with Darco. The brown solid from the cold solution was recrystallized several times from water to yield 2-aminobenzimidazole *m*-aminobenzenesulfonate, m.p. 178–180° (dec.). The yield of purified material was 11.5 g. (51%).

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[5] Analyses by Miss Theta Spoor and Mr. Howard Clark.

[6] This product was first prepared in this laboratory by Dr. David Y. Curtin.

Anal. Calc'd for $C_{13}H_{14}N_4O_3S$: C, 50.94; H, 4.61; N, 18.29.
Found: C, 50.91; H, 4.61; N, 18.10.

In order to verify the salt structure of this material, the dilute aqueous solution of the sulfonate was treated with an aqueous solution of sodium picrate. The fluffy yellow needles, which were obtained immediately, turned brown at 254–274° and melted at 278–279° (dec.). No depression in melting point was observed when this material was mixed with an authentic sample of the picrate of 2-aminobenzimidazole.

2-Benzenesulfonamidobenzimidazole. A mixture of 2.7 g. (0.025 mole) of *o*-phenylenediamine and 5.0 g. (0.025 mole) of benzenesulfonylguanidine was heated in a metal-bath maintained at 190° for two and one-half hours and at 215–225° for two and one-half hours. At this point the mixture had begun to solidify and a tarry odor was noted. The cold reaction product dissolved almost completely in 2 *N* sodium hydroxide after standing one-half hour. The small amount of insoluble material was removed and the filtrate was made slightly acidic with hydrochloric acid. The solid which appeared in the acidified solution weighed 3.8 g. (56%). It was purified by washing with warm water and warm ethanol. The residue was recrystallized from glacial acetic acid to yield white crystals of 2-benzenesulfonamidobenzimidazole, m.p. 354–356° (block) with slight sintering at 344°.

Anal. Calc'd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 3.94.
Found: C, 57.12; H, 3.94.

When the above filtrate from the isolation of the desired material was exactly neutralized, a solid precipitated which weighed 0.8 g. and melted at 131–134°. After purification by recrystallization from water the material melted at 144–145°. Its composition corresponded to that of a trihydrate of 2-aminobenzimidazole benzenesulfonate.

Anal. Calc'd for $C_{13}H_{13}N_3O_3S \cdot 3H_2O$: C, 45.25; H, 4.92; N, 12.15.
Found: C, 45.24; H, 4.50; N, 11.55.

A very low yield of the desired product was obtained when this reaction was carried out in ethylene glycol at a bath temperature of 190° for two hours and 220° for two additional hours More than half of the benzenesulfonylguanidine was recovered unchanged.

2-(m-Nitrobenzenesulfonamido)benzimidazole. A solution of 7.3 g. (0.03 mole) of *m*-nitrobenzenesulfonylguanidine (see below) and 3.24 g. (0.3 mole) of *o*-phenylenediamine in 30 cc. of quinoline was heated under gentle reflux in a metal-bath maintained at 255–260°. The heating was continued for two and one-half hours. Evolution of ammonia had become appreciably slower after the first hour, but the gas at the top of the condenser was still basic to litmus after two hours. The cooled solution was poured into 200 cc. of methanol and allowed to stand at 0° until precipitation was complete. The brown precipitate was washed with a small amount of methanol. It was taken up in 60 cc. of 2 *N* sodium hydroxide and filtered from a small amount of insoluble material. The filtrate was neutralized with dilute hydrochloric acid and the grey precipitate was recrystallized from ethanol in which it was only difficultly soluble. From the cold ethanol solution was obtained 2.6 g. (27%) of white 2-(*m*-nitrobenzenesulfonamido)benzimidazole, m.p. 299–301° (dec.).

Anal. Calc'd for $C_{13}H_{10}N_4O_4S$: C, 49.05; H, 3.17.
Found: C, 49.05; H, 3.28.

Various methods for improving the yield of the reaction were attempted. The absence of any diluent resulted in the formation of a black tar which was not appreciably soluble in sodium hydroxide. This result was observed after heating thirty minutes at 215°, two hours at 205–210°, or four hours at 200–210°. Ethylene glycol did not appear to be a suitable substitute for quinoline

2-Metanilylbenzimidazole. To a stirred suspension of 6 g. of iron dust in 50 cc. of refluxing ethanol was added 2.8 cc. of 6 *N* hydrochloric acid and 2.0 g. (0.006 mole) of 2-(*m*-nitrobenzenesulfonamido)benzimidazole. The mixture was heated on a water-bath for five hours. The hot solution was filtered and about half of the ethanol was removed under a jet of air and an equal volume of water was added. The solid which appeared was recrystallized from Cellosolve-water The purified 2-metanilylbenzimidazole melted above 325°.

Anal Calc'd for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20.
Found: C, 54.43; H, 4.42.

2-Sulfabenzimidazole. A mixture of 5.4 g. (0.025 mole) of sulfaguanidine and 2.7 g. (0.025 mole) of *o*-phenylenediamine was heated in a metal-bath maintained at 190° for two hours and at 240° for one hour. The black product was treated twice with 30 cc. of 5% sodium hydroxide and filtered from insoluble material. The filtrate was made just acidic with acetic acid and the light solid separated. The product was soluble in alkali or acid. It was only slightly soluble in ethanol, methanol, glacial acetic acid, or water. After one recrystallization from ethanol and two from water, white micro-needles of 2-sulfabenzimidazole melted with decomposition at 321–322°.

Anal. Calc'd for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20.

Found: C, 54.28, 54.00; H, 4.15, 4.16.

Guanidine m-nitrobenzenesulfonate. To a solution of 15 g. (0 0835 mole) of guanidine carbonate dissolved in 175 cc. of water containing 32 g. of sodium hydroxide was added with cooling and stirring 52 g. (0.235 mole) of *m*-nitrobenzenesulfonyl chloride. Stirring was continued overnight. The reaction mixture was filtered and the yellow solid washed with 200 cc. of cold water and recrystallized from 500 cc. of ethanol to yield 34 g. (60%) of yellow material. By recrystallization from ethanol white crystals, m.p. 188–189°, were obtained.

Anal. Calc'd for $C_7H_{10}N_4O_5S$: C, 32.06; H, 3.84; N, 21.37.

Found: C, 32.32; H, 3.84; N, 21.42.

When the reaction was carried out with twice the amount of sodium hydroxide in the same amount of water the results were entirely analogous. A reaction similar to this latter one showed *p*H 10.5 before the addition of the sulfonyl chloride, 9.8 immediately after all sulfonyl chloride had been added and then a gradually rising *p*H which reached 10.6 after two hours.

m-Nitrobenzenesulfonylguanidine. *m*-Nitrobenzenesulfonamide (5) was produced from the sulfonyl chloride and aqueous ammonia and isolated by removal of ammonia and some of the water *in vacuo*. After one recrystallization from ethanol 82–89% of *m*-nitrobenzenesulfonamide, m p. 162.5–164°, was obtained.

In a metal-bath at 205–210° was placed an Erlenmeyer flask containing 10.7 g. (0.05 mole) of *m*-nitrobenzenesulfonamide. When the solid had melted, 4.2 g. (0.05 mole) of dicyanodiamide was added with stirring during thirty minutes. Heating and stirring were continued for a total of two hours and the reaction mixture was allowed to cool to a yellow glass. This was boiled with 300 cc. of water and the hot solution was filtered from the insoluble residue. In the cold filtrate appeared a gummy material which was converted to a clean solid by the addition of 30 cc. of 3 *N* sodium hydroxide. The crude product was purified by washing with 2 *N* sodium hydroxide and then with cold water. The residue was recrystallized once from water and once from ethanol to yield 5.1 g. (42%) of sparkling white crystals of *m*-nitrobenzenesulfonylguanidine, m.p. 195–198°.

Anal. Calc'd for $C_7H_8N_4O_4S$: C, 34.42; H, 3.30.

Found. C, 34 49; H, 3.29.

A great many variations in procedure were tried. Little effect was noticed when two or three equivalents of dicyanodiamide were used. A heating time of eight or twenty-five hours lowered the yield appreciably. One hour or less was insufficient heating time even though the bath was maintained at 235–240°.

Metanilylguanidine. The reduction was accomplished by adding 5.4 g. of *m*-nitrobenzenesulfonylguanidine to a suspension of 22 g. of iron dust in 100 cc. of ethanol containing 8 cc. of 6 *N* hydrochloric acid. The reaction mixture was boiled under reflux with stirring for six to seven hours and the hot solution was filtered several times to remove most of the iron. The filtrate was evaporated under a jet of air to a volume of 75 cc. and again filtered to remove ferric hydroxide. The cooled filtrate produced 2.7 g. (59%) of long thin needles, m.p. 175–181°. After two recrystallizations from ethanol, white metanilylguanidine melted to an orange liquid at 180–181°.

Anal. Calc'd for $C_7H_{10}N_4O_2S$: C, 39.24; H, 4.71.

Found: C, 39.42; H, 4.81.

2-Benzenesulfonamido-4-hydroxy-7-chloroquinazoline. A mixture of 5.0 g. (0.025 mole) of ethyl *p*-chloroanthranilate and 5.0 g. (0.025 mole) of benzenesulfonylguanidine was heated in a metal-bath. The mixture became molten at 205° and rapid evolution of ammonia began at 245°. The melt was heated at 250–260° for one hour. The cold solid was slurried twice with 50 cc. of 3 *N* sodium hydroxide and the combined filtrates were acidified with dilute hydrochloric acid. The precipitate from the acidified solution was boiled with water and with a small amount of ethanol. The residue was recrystallized from ethanol several times to produce white shining plates, m.p. 284.5–286°.

Anal. Calc'd for $C_{14}H_{10}ClN_3O_3S$: C, 50.08; H, 3.00, N, 12.52.
Found: C, 50.27; H, 3.15; N, 12.63.

SUMMARY

The reaction of 2-aminobenzimidazole with a sulfonyl chloride has been shown to proceed at a ring nitrogen atom to produce the 1-sulfonyl derivative.

It has been found that 2-sulfonamidobenzimidazoles may be prepared by heating a sulfonylguanidine with *o*-phenylenediamine.

URBANA, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS OF THE JOHNS HOPKINS UNIVERSITY]

SULFONAMIDE PREPARATIONS IN GLACIAL ACETIC ACID[1]

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The preparation of N^1-halophenyl-N^4-acetylsulfanilamides in the usual media, pyridine (1) and dimethylaniline (2), was found to be accompanied by undesirable side-reactions. This communication reports the results of an investigation of sulfonamide synthesis carried out in these and other media in an effort to overcome this difficulty. In particular, the scope of application of glacial acetic acid and its limitations with respect to this synthesis will be presented.

Interest in the sulfanilanilides was aroused by the reported (1c) activity of the 3′,5′-dihalo derivatives in a malarial infection in canaries and this work was undertaken in order to prepare a series of sulfonanilides for antimalarial investigation. The 3′,5′-dihalosulfanilanilides were found to possess activity which was retained in the presence of *p*-aminobenzoic acid when tested against a *Plasmodium lophurae* infection in the duck. This was in marked contrast to other sulfanilamides (3) such as sulfadiazine. Another contrasting characteristic was their activity against a *Plasmodium cathemerium* infection in the duck where the usual sulfanilamides are relatively inactive. The details of this work and the activity of a series of sulfonanilides against these two experimental malarial infections are being reported elsewhere (4).

The side-reactions in pyridine, in pyridine-acetone or in dimethylaniline were most troublesome with haloanilines. For example, the tenacity of the contaminants is illustrated by the fact that colorless products of sharp melting point showed ultraviolet fluorescence not characteristic of later preparations by a different method. Consideration of the base strength of aniline in glacial acetic acid (5) and the ready acylation of anilines in this solvent (6) suggested its examination as a medium for the preparation of sulfonamides. Since this work was completed, certain preparations in acetic acid have been reported by Allen *et al.* (7). N-Acetylsulfanilyl chloride was found to have high solubility (footnote b, Table I) in boiling acetic acid and to be stable to the one-half per cent of water present. In contrast to the rapid decomposition of sulfonyl chlorides in pyridine solution, one mole of added water produced only a slow reaction in hot acetic acid as evidenced by the high recovery of N-acetylsulfanilyl chloride. However, the presence of bases such as sodium acetate or pyridine caused very rapid hydrolysis of the sulfonyl chloride in acetic acid while the effect of acetamide or urea was distinctly less rapid. These results are in general agreement with the base strengths (5) in this medium and with the assumption of an acetate ion catalysis. Thus, the weakest base, water, is capable *per se* of producing only a very slow reaction. With one mole of anhydrous sodium acetate, the theoretical amount of sodium chloride was quickly precipitated and another mole caused the separation of material identified as sodium acetylsulfanilate.

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In further study of the reactions of sulfonyl chlorides in acetic acid, the group of experiments summarized in Table I was carried out. The first result indicates that half of the aniline is converted by the strong hydrochloric acid to a completely unreactive form, presumably the anilinium ion. Consequently, the reactive anilinium acetate solution must contain appreciable amounts of aniline base[3] in equilibrium. This would be expected of the "transition" bases in acetic acid as Hall (5) has pointed out. In view of the rapid hydrolysis already mentioned, it was expected that the improved yield with sodium acetate would be greatest if the base were added in ½, ¼, ⅛, etc., molar quantities in a stepwise fashion (third line—Table I). Thus, the replacement of the weakly basic chloride ion by the strongly basic acetate ion sufficiently shifts the equilibrium of the anilinium ion to the side of aniline base to permit further reaction. Acetamide is too weak a base (5) to function similarly and apparently does not form an insoluble hydrochloride. The general superiority of sodium acetate and of the use of a base in fractional equivalents is obvious from these data. When readily available, the aniline itself would serve as a suitable base and this procedure would be expected to give optimum yields from an expensive sulfonyl chloride (line 5—Table I).

TABLE I

COMPARISON OF DIFFERENT METHODS OF PREPARATION OF SULFONANILIDES IN ACETIC ACID[a]

SULFONYL CHLORIDE	AMINE	BASE	% YIELD
ASC[b] or BSC[c]	1 mole aniline	none	50
ASC or BSC	1 mole aniline	NaOAc initially[d]	65
ASC or BSC	1 mole aniline	NaOAc stepwise[e]	90
ASC or BSC	1 mole aniline	Acetamide stepwise[e]	50
ASC or BSC	2 moles aniline	Aniline	98
ASC	3,5-dichloroaniline	NaOAc stepwise[e]	87
ASC	3,5-dichloroaniline	Pyridine stepwise[e]	gum[f]

[a] Hereafter understood to mean the commercial 99.5% material.

[b] ASC = N-acetylsulfanilyl chloride; solubility, at least 100 g./100 cc.

[c] BSC = Benzenesulfonyl chloride.

[d] Addition of 1-2 moles of anhydrous sodium acetate preceded the addition of the sulfonyl chloride to the aniline solution.

[e] The base was added in fractional equivalents as the reaction proceeded, in the manner described in detail in the experimental section.

[f] The same *weight* of alkali-soluble brown gummy product was obtained as in the line above.

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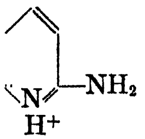
[3] This interpretation assumes the reactivity of an amine to be based on the availability of the nitrogen electron pair for sharing with the sulfonyl group to form an unstable transitory intermediate, the sulfonylammonium ion.

In regard to acetylation as an interfering side reaction, the use of hot acetic acid and anhydrous sodium acetate might be expected to produce acylation by formation of acetyl chloride, acetic anhydride or benzenesulfonic-acetic anhydride (8). The acid catalysts present, the sulfonic and hydrochloric acids, would increase the likelihood of acetylation especially with weakly basic anilines (6). Although the yields of sulfonanilides were high, an examination of the mother liquors was made to determine the extent of acetylation. In the case of acetylsulfanilanilide, about a 0.5% yield of acetanilide was isolated but a benzenesulfonanilide preparation failed to give any evidence of acylation.

The satisfactory results obtained with various sulfonyl chlorides and anilines in acetic acid are illustrated in Table II. The reactions are rapid and the use of this medium enables direct isolation by crystallization from a very effective purification solvent.

Although pyridine has been generally used for sulfanilanilide syntheses (1), an anhydrous medium appears to be necessary only with weakly basic anilines. For example, aniline and *p*-anisidine were found to couple equally well in such widely differing solvents as water, pyridine, and acetic acid. While the weaker base (5, 9), *p*-chloroaniline, also coupled well in water or acetic acid, *p*-nitroaniline gave no sulfonanilide in aqueous acetone. The 56% yield of N^1-4-nitrophenyl-N^4-acetylsulfanilamide in acetic acid compares favorably with the 40% yield reported in dimethylaniline (2). Similarly, 3,5-dibromoaniline showed no coupling in water but reacted in either acetic acid or pyridine. To determine the scope of application of the acetic acid medium, amines of other types were studied. Failure to couple was observed with the acyclic bases, ammonia, diethylamine, and guanidine, and the heterocyclic amines, 2-amino-thiazole, -pyridine, and -pyrimidine, and 4-aminoquinoline. In addition, the two amides, urea and acetamide, represent another unreactive group since no sulfonamide of the type $CH_3CONHC_6H_4SO_2NHCOR$ was formed.

It is seen from these results that the use of acetic acid extends coupling into the range of anilines too weak to couple in water. This effect of the medium with these weak amines is apparently due to their low reactivity which, in water, permits rapid hydrolysis of the sulfonyl chloride. As a result of the base-strengthening effect of an acidic solvent, strong bases such as diethylamine which couple satisfactorily in water are completely ionized in acetic acid and thus fail to react.[3] The general behavior of the α- and γ-aminoheterocycles may be represented by 2-aminopyridine which is unreactive in acetic acid, slightly reactive in water, and quite reactive in pyridine (10). For amines of this basicity (11), lack of reaction would result from the formation of the resonating ion

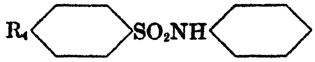


in acetic acid. In water, the high reactivity (12) of the ring-nitrogen would produce a water-sensitive substance and consequently hydrolysis of the sulfonyl chloride as the main reaction. Where the stability of the ring

N-sulfonyl derivatives is greater than in the present instance, their isolation has been accomplished in large (13) or predominating (14) amounts. With the formally analogous amidines, this difficulty would not be encountered since reaction on either nitrogen of the free base would produce the same product

TABLE II

Preparation of Sulfonanilides in Glacial Acetic Acid[a]



R_4	N^1-PHENYL SUBSTITUENTS	YIELD, %[b]	M.P.[c] °C.	REPORTED M.P.
CH_3CONH	H	90	214–215	214[d, k]
CH_3CONH	Cl_2-3,5	87	239–240	239–240[e, f]
CH_3CONH	Br_2-3,5	83	242–243	238–239[e, f]
CH_3CONH	Cl_3-3,4,5	85	272–273	271[e]
CH_3CONH	OCH_3-2	84	212–213	212[g]
CH_3CONH	OCH_3-3	68	192–193	193[g]
CH_3CONH	OCH_3-4	90	200–201	200[g, h]
CH_3CONH	NO_2-3	74	244–245	244[g, k, m]
CH_3CONH	NO_2-4	56	263–264	264[g, k, l, m, n]
CH_3CONH	$NHCOCH_3$-4	50	293–294	[m]
NO_2	Br_2-3,5	92	175–176	172[e]
H	H	89	112–113	110–112[p]
H	Cl-4	91	122–123	121–122[f, q]
H	Br_2-3,5	77	130–131	130–131[f]

[a] Using sodium acetate stepwise as in the procedure described in the Experimental Section.

[b] Product crystallized from reaction medium melting within 5° of the pure substance.

[c] Corrected. The identity of the products was further confirmed by hydrolysis or reduction in good yield to sulfanilanilides having the melting points reported in the references given.

[d] Gelmo, *J. prakt. Chem.* (2) **77**, 374 (1908).

[e] See ref. 1c.

[f] Kaplan and Leubner, *J. Am. Chem. Soc.*, **67**, 1076 (1945).

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[l] Kaufmann and Bückmann, *Arch. Pharm.*, **279**, 194 (1941).

[m] See ref. 2.

[n] See ref. 1d.

[p] Zief and Mason, *J. Org. Chem.*, **8**, 4 (1943).

[q] Wallach and Huth, *Ber.*, **9**, 426 (1876).

In pyridine, the amine would be present solely as the reactive free base, as would be the case in an aprotic solvent such as benzene. In many cases, pyridine performs an independent additional function of preventing the formation of the unreactive ion by the hydrochloric acid produced in the reaction. For this function, sufficiently strong heterocyclic amines require the use of the stronger base, triethylamine, in pyridine to permit more than a partial reaction (15). Finally, the amides and sulfonamides represent a group too weakly basic to react (16) except under conditions permitting negative ion formation (16, 17).

In the hope of finding a sulfonylating agent more reactive toward anilines than the sulfonyl chlorides, the behavior of a sulfonic anhydride was studied. Since previous syntheses of benzenesulfonic anhydride produce variable results (18), a method previously used (19) on activated halogen compounds such as benzotrichloride, benzal chloride, and acyl halides was tried. The reaction of benzenesulfonyl chloride with anhydrous oxalic acid produced the desired anhydride, presumably according to the following equation:

$$2C_6H_5SO_2Cl + (COOH)_2 \rightarrow (C_6H_5SO_2)_2O + 2HCl + CO + CO_2.$$

This reaction may be written as occurring in two steps: first, hydrolysis of one mole of acid chloride to the anhydrous acid and, second, the reaction of the latter with unchanged acid chloride. However, the special function of the oxalic acid was indicated by the failure to obtain the anhydride from the sulfonyl chloride and anhydrous sulfonic acid even under more drastic conditions. Likewise, in the case of acyl chlorides, Anschütz (19) demonstrated that oxalic acid produces anhydrides at temperatures which do not cause reaction of the acid chloride with the corresponding acid. The purified crystalline benzenesulfonic anhydride produced in this way reacted rapidly in hot acetic acid with two moles of aniline to give an 81% yield of sulfonanilide. However, this work was interrupted before the usefulness of this preparation and the behavior of the anhydride toward relatively unreactive anilines were investigated.

When ethyl benzenesulfonate was treated with aniline in acetic acid at 100–120°, about 1% of benzenesulfonanilide was formed in addition to the main product, ethylaniline.

The results of these sulfonamide studies suggest certain applications of an acidic reaction medium. The use of this method for the preparation of sulfonanilides for identification purposes (20) would be of interest, particularly in view of the observed lack of disulfonamide formation. Another field of application would be in the separation of amines which react with sulfonyl chlorides in acetic acid from those which are unreactive (*e.g.*, aliphatic and heterocyclic amines from anilines). From their general "benzenoid" chemical reactions (21) and their lower base constants (11), one might expect the β-amino heterocycle group to react in acetic acid similar to the anilines. Separations within the anilines themselves would seem feasible where suitable differences in basicity are present (*e.g.*, *o*- and *p*-nitroaniline). Sharper separations than are possible in acetic acid may be obtainable through the use of a more strongly acid medium such as the halogenated acetic acids.

A search for a convenient preparation of 3,5-dibromoaniline on a relatively large scale has led to the method described in the Experimental Section. This procedure utilizes preparative methods better suited to the three steps involved than those used in previous work. The method of Fuchs (22) starting from 4-aminoacetanilide is less satisfactory chiefly because of the oxidative side-reaction in the initial bromination step.

EXPERIMENTAL

General procedure for preparations in acetic acid. Sulfonanilide formation was essentially complete in five to ten minutes at 100–120° in acetic acid and this period of time was allowed between sodium acetate additions. Upon completion of the reaction, the very insoluble (about 0.05% at the boiling point) sodium chloride can be separated from the product by filtration or dissolved by judicious addition of water. Depending on the amount of acetic acid employed, the sulfonanilides either crystallize during the reaction or do so on cooling. While recrystallized N-acetylsulfanilyl chloride was preferred, crude material[4] gave equally good results if dissolved in hot acetic acid and filtered (20–30% insoluble) prior to addition of the amine.

The aniline solution in glacial acetic acid (400–1,000 cc./mole) was heated to 100° and treated with the sulfonyl chloride (usually in 25% excess), which raised the temperature to the boiling point. With some anilines such as 3,5-dibromoaniline, a crystalline precipitate of the amine hydrochloride separated within five minutes. Immediately after the first sodium acetate addition, these crystals, if present, redissolved and in all cases sodium chloride precipitated as a fine powder. At intervals of five to ten minutes beginning with the mixing of the reagents, finely powdered commercial anhydrous sodium acetate was added in $\frac{1}{2}$, $\frac{1}{4}$, $\frac{1}{8}$, and $\frac{1}{8}$ molar quantities. A final treatment with $\frac{1}{4}$ mole was made and fifteen minutes allowed before isolation. After each addition the mixture was momentarily brought to boiling and then maintained at 100° between additions. By rapid addition of water while vigorously shaking, the reaction slurry could usually be made to clear completely before crystallization began. After cooling, the product was filtered and washed with cold 60% acetic acid, 5 *N* hydrochloric acid and water. The 2–15% of material present in the filtrate may be recovered by further aqueous dilution. The anilides were purified by recrystallization from 40–100% acetic acid or 40–95% ethanol.

Acetylation by-products. From a 0.2-mole preparation of N^1-phenyl-N^4-acetylsulfanilamide, the acetic acid mother liquor and washings were evaporated to dryness at 25° in a stream of air. The residue was finely powdered and suspended in cold 0.5 *N* sodium hydroxide and quickly filtered. The process was then repeated with cold 0.1 *N* hydrochloric acid. The tan residue amounting to a 0 5% yield melted at 112–114°. Recrystallization from water gave a 90% recovery of material having the melting point 114–115° which was not depressed by authentic acetanilide of the same melting point.

A similar procedure applied to a benzenesulfonanilide preparation gave no acetanilide after isolation of the sulfonanilide in 89% yield. When one gram of acetanilide was carried through this isolation procedure the recovery was 90%.

Even the small amount of acetylation indicated by the first result might be explained by assuming about 0.2% acetanilide as impurity in the recrystallized N-acetylsulfanilyl chloride.

Products from N-acetylsulfanilyl chloride and sodium acetate. Treatment of 3.9 g. (0 017 mole) of N-acetylsulfanilyl chloride in 10 cc. of hot acetic acid containing 0.3 g. (0.017 mole) of water with 1.35 g. (0.017 mole) of anhydrous sodium acetate gave 0 9 g. (90%) of precipitated sodium chloride. The use of another equivalent of sodium acetate gave 3.6 g. of precipitate which was insoluble in acetone and very soluble in water Hydrolysis with 2 *N* hydrochloric acid for two hours gave 99% of the theoretical arylamine (23) calculated for sodium N-acetylsulfanilate. A 1.5-g. sample was hydrolyzed with concentrated hydrochloric acid at 100° for two hours and an 80% yield of sulfanilic acid isolated.

Benzenesulfonic anhydride. Anhydrous oxalic acid was prepared from C.P. crystalline dihydrate by oven drying (24) of the powder at 115°. After two hours, the rate of weight loss had decreased precipitously and acidimetric analysis gave an equivalent weight of 44.9 (calc'd: 45.0); yield: 99%.

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[4] Both the laboratory preparations ("Organic Syntheses", Coll. Vol. I, 8) and the commercial product contain an amount of acetic acid-insoluble material which increases with time.

A mixture of 4.5 g. (0.05 mole) of powdered anhydrous oxalic acid and 17.7 g. (0.1 mole) of freshly distilled benzenesulfonyl chloride showed a distinct change in the nature of the solid present on warming to 100°. Evolution of gas began at 150° and was allowed to proceed to completion at 160°. After brief heating to 200°, volatile material was removed at 180° under 100 mm. pressure. The liquid residue was then shaken intermittently during one-half hour at 180° under 10 mm. pressure. The liquid residue (6.8 g., 46% yield) crystallized quickly on cooling. In contrast to anhydrous benzenesulfonic acid, this material did not deliquesce in air and was not soluble in cold water or dilute alkali. The initial melting point of 78° was raised to 92° by recrystallization from specially dried anhydrous alcohol-free ether. The observed acidimetric equivalent weight of 143 (calc'd: 149) confirmed its identity.

Reaction of benzenesulfonyl chloride and anhydrous sodium acetate at 230° for one hour gave a distillate coming over at 140–155°. By fractional distillation, this material was shown to be a mixture of acetyl chloride, acetic acid, and acetic anhydride. Although the production of these substances suggests the possibility of acetylation, this side-reaction in hot acetic acid was not apparent in general. The reaction residue consisted of sodium benzenesulfonate and unchanged sulfonyl chloride.

Anhydrous benzenesulfonic acid (25) was conveniently prepared by azeotropic distillation of the solution of the hydrate in benzene and vacuum evaporation to dryness. When this material was heated with one mole of benzenesulfonyl chloride at temperatures up to the decomposition point (about 300°), no appreciable evolution of hydrochloric acid was observed. Vacuum distillation gave unchanged acid chloride and an unpromising tarry residue.

Benzenesulfonanilide from ethyl benzenesulfonate. To a solution of 9.3 g. (0.1 mole) of aniline in 50 cc. of acetic acid at 90° was added 17.6 g (0.1 mole) of ethyl benzenesulfonate. A rapid reaction occurred with evolution of heat. After half an hour, the mixture was diluted with 150 cc. of 1 *N* hydrochloric acid and the clear solution extracted with five 100-cc portions of ether. This extract was shaken with solid sodium bicarbonate before treatment with 25 cc. of 2 *N* sodium hydroxide. The aqueous layer gave a white precipitate on acidification. Weight: 0 24 g. (1% yield); m.p. 114° not depressed by authentic benzenesulfonanilide.

The acidic aqueous layer above was treated with one liter of 60% potassium hydroxide and extracted with five 100-cc. portions of ether. The extract on evaporation gave a syrupy residue which was treated in aqueous acetone with sodium hydroxide and *p*-toluenesulfonyl chloride. After dilution with water, the solid was filtered and recrystallized from dilute alcohol. The observed melting point of 88° checks that given by Otto (26) for N-(*p*-toluenesulfonyl)-N-ethylaniline.

2,6-Dibromo-4-nitroaniline (27). A solution of 224 g. (1.62 moles) of *p*-nitroaniline (Eastman Technical) in 2 liters of glacial acetic acid at 65° was vigorously stirred during the addition of 520 g. (3.26 moles) of bromine in 1200 cc. of acetic acid within four hours. A very heavy precipitate formed after about one-third of the bromine had been added and was redissolved by 200 cc. of warm water. The subsequent precipitation, however, was not affected by addition of water. During the bromine addition, the temperature dropped slowly and was brought up to 55° for a final half-hour's stirring. The reaction mixture was poured with stirring into a slurry of 6 liters of water and 2 kg. of ice. After thorough washing with water and air-drying the light yellow product weighed 455 g. (95%) and melted at 204–206° (sintering at 201°).

2-Nitroaniline was brominated equally well by the same procedure. The resulting dibromide (28) was used as an alternative intermediate for the next step.

3,5-Dibromonitrobenzene (29). An acetic acid suspension of 2,6-dibromonitroaniline (250 g.) was diazotized with nitrosylsulfuric acid using the procedure of Hodgson and Walker (30). The ethanol deamination of Hodgson and Turner (31) was followed in detail except that optimum yields were obtained only when about one-twelfth as much cuprous oxide was used. Recrystallization from alcohol or ethylene dichloride gave a 70% yield of material melting at 106°. The use of formic acid or of ethylene chlorhydrin gave lower yields [*cf.* Hodgson and Turner (32)].

Hypophosphorous acid deamination (33) is an equally satisfactory preparative method but the bisulfite-nitric acid method of Witt (34) gave lower yields.

3,5-Dibromoaniline (29). Catalytic reduction of 3,5-dibromonitrobenzene with Raney nickel (35) at atmospheric temperature and pressure was complete in five hours. The commercial nickel catalyst, available in pellet form, was inactive under these conditions. A thick slurry of 141 g. of nitro compound and 10 g. of Raney nickel catalyst in 280 cc. of absolute alcohol was shaken in a one-liter bottle under hydrogen. After filtration of the solution, addition of one volume of water caused crystallization of 101 g. (80%) of amine melting at 56–57°.

Reduction with stannous chloride in acetic acid followed by basification and extraction with ethylene dichloride produced pure amine in 64% yield. However, sodium hydrosulfite reduction gave only a 25% yield.

3,4,5-Trichloroaniline (36). Eastman 2,6-dichloro-4-nitroaniline was converted to 3,4,5-trichloronitrobenzene by the Sandmeyer procedure of Hodgson and Walker (30). The amine was prepared in 70% yield by Raney nickel reduction as described above. The specificity of Raney nickel in the reduction of such activated halogen compounds has been reported by Winans (37).

Materials. The American Cyanamid Company supplied the N-acetylsulfanilyl chloride, 2-amino-pyridine, -thiazole, -pyrimidine, and 4-aminoquinoline used in this work. A sample of 3,5-dichloroaniline was furnished by the E. I. du Pont de Nemours Company. Other reagents were those obtained from the Eastman Kodak Company.

SUMMARY

Glacial acetic acid has been shown to be a satisfactory medium for the preparation of sulfonanilides accompanied by a minimum of by-product formation.

The limitations of application of various reaction media have been discussed in relation to the mechanism of sulfonamide synthesis.

Possible applications of an acidic solvent to sulfonamide preparation and amine separations have been indicated.

A new type of synthesis of sulfonic anhydrides has been successfully carried out for benzenesulfonic anhydride.

Benzenesulfonanilide was formed in small amount from aniline and ethyl benzenesulfonate in acetic acid.

An improved procedure for the preparation of 3,5-dibromoaniline has been described.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

NUCLEAR SUBSTITUTED MORPHINE DERIVATIVES

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The introduction of organic radicals into ring III of the morphine nucleus has heretofore been accomplished through reaction of the Grignard reagent with derivatives having a double bond in conjugation with the cyclic ether oxygen, as in dihydrothebaine or dihydrocodeinone enol acetate (1). In these reactions the ether ring is invariably opened. The carbonyl group of the morphine ketones is inexplicably inert toward RMgX compounds. Codeinone does not react with methylmagnesium iodide up to 170° (2); dihydrocodeinone is recovered nearly quantitatively under ordinary conditions (3), but if the reaction is forced, behaves like the 6,7-unsaturated types, to give, for example methyldihydrothebainone (4), in which the carbonyl group is still present.[2] Pseudocodeinone likewise suffers rupture of the ring, with retention of the carbonyl, and dihydropseudocodeinone is completely indifferent (3).

In view of the greater activity of organolithium compounds (5), it was of interest to investigate their action upon some of these recalcitrant ketones. The mode of addition proved to be radically different from that of Grignard reagents, and resulted, in most instances, in excellent yields of tertiary carbinols in which the new organic group can scarcely be other than at the 6 position. The reaction thus makes available entirely new types of nuclear substituted morphine derivatives for chemical and pharmacological studies.

With dihydrocodeinone (I) and methyllithium in ether, reaction took place instantaneously at 0°, giving an almost quantitative yield of 6-methyldihydrocodeine (II). Although a new asymmetric center was created at C-6, only the one diastereomer was formed, as was true in the other reactions studied. Whereas 6-methyldihydrocodeine was easily crystallized, and formed a series of well-crystallized salts, as the organolithium reagent was changed from methyl to phenyl, ethyl, *n*-amyl, the properties of the products became progressively less favorable. 6-Phenyldihydrocodeine could not be crystallized, but formed good salts, the resinous ethyl compound gave only a methiodide and picrate, and no crystalline derivative of the *n*-amyl compound could be obtained.

The reaction of methyllithium with 1-chloro- and 1-bromo-dihydrocodeinones proceeded smoothly without elimination of the halogen atom, and the resulting 1-halo-6-methyldihydrocodeines were obtained in good yield. Although halogen-metal interconversion has been observed with the halogenated anisoles (6), the halogen in the halodihydrocodeinones is apparently not reactive enough to be affected under the conditions used.

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[2] In a private communication received after this manuscript had been accepted for publication, we are informed by A. H. Homeyer and J. A. Caughlan of the Mallinckrodt Chemical Works that methylmagnesium chloride can be caused to act on dihydrocodeinone to form 6-methyldihydrocodeine. We have identified their product by mixed melting point and rotation Footnote added Nov. 14, 1946.

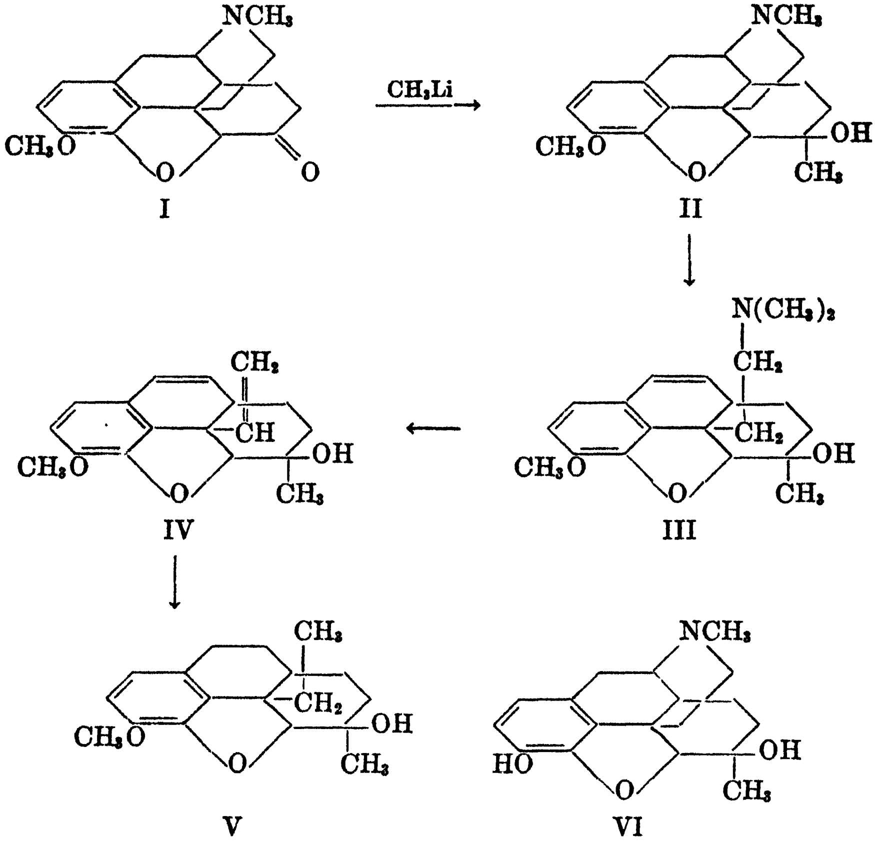
Cleavage of the methoxyl group of 6-methyldihydrocodeine, to arrive at the morphine analog, was unsuccessful; with the usual acidic and alkaline demethylating agents, only resinous products were formed. In attempting to proceed through dihydromorphinone-3-methoxymethyl ether, it was observed that the sodium salt of dihydromorphinone is quite soluble in ether. The methyllithium reaction was therefore applied to dihydromorphinone itself, using sufficient reagent to compensate for that consumed by the phenolic hydroxyl. The lithium salt was freely soluble in ether, permitting reaction of the carbonyl, to give the desired 6-methyldihydromorphine (VI). Etherification of the phenolic group with diazomethane gave 6-methyldihydrocodeine, identical with that from the dihydrocodeinone reaction.

The tertiary alcoholic group of 6-methyldihydrocodeine, as expected, was difficult to acetylate. Acetyl chloride in pyridine, and acetyl chloride and magnesium in ether (7) left it unaffected. A modification of the method of Houben (8), using methyllithium and treating the lithium salt with acetic anhydride, gave the ester, 6-methyl-6-acetyldihydrocodeine, demonstrating the presence of the alcoholic hydroxyl.

The Hofmann degradation of 6-methyldihydrocodeine methiodide with 30% KOH gave in the first step 6-methyldihydromethylmorphimethine (III). The methiodide of this resisted wet degradation, and it was necessary to resort to dry-distillation (under a vacuum) of the methohydroxide to obtain the nitrogen-free product (IV), 6-methyl-6-hydroxy-13-vinylhexahydromethylmorphenol; for consistency with previous work we retain the nomenclature of morphine chemistry. Catalytic reduction of IV (2 moles of hydrogen) gave the corresponding 13-ethyloctahydromethylmorphenol derivative (V).

Replacement of the alcoholic hydroxyl of 6-methyldihydrocodeine by chlorine was attempted with the intention of proceeding through 6-methylchlorodihydrocodide by dehydrohalogenation to the pharmacologically interesting desoxycodeine types. Heating with conc'd HCl in a sealed tube after the method of Knorr and Hörlein (9) gave unchanged material. When, however, the carbinol was refluxed in chloroform with thionyl chloride, a new product which contained no chlorine was isolated in 65% yield. It was non-phenolic, and decolorized potassium permanganate in acetone slowly. Analysis established it to be a 6-methyldesoxycodeine, resulting from loss of a molecule of water from 6-methyldihydrocodeine, or of hydrogen chloride from an intermediate 6-methylchlorodihydrocodide. Such a facile transformation is surprising, in view of the failure of dihydrocodeine or dihydroisocodeine to undergo a parallel change, and the drastic treatment required to remove hydrogen chloride from chlorodihydrocodide (10). The compound was assigned the structure of 6-methyldesoxycodeine-C (VII) on the basis of these observations: Alkali-insolubility and negative diazosulfanilic acid test showed that the oxygen bridge was not ruptured. On ozonolysis it gave no formaldehyde, but treatment of the ozonolysate with iodine and alkali yielded iodoform, indicating that the unsaturation is endocyclic,

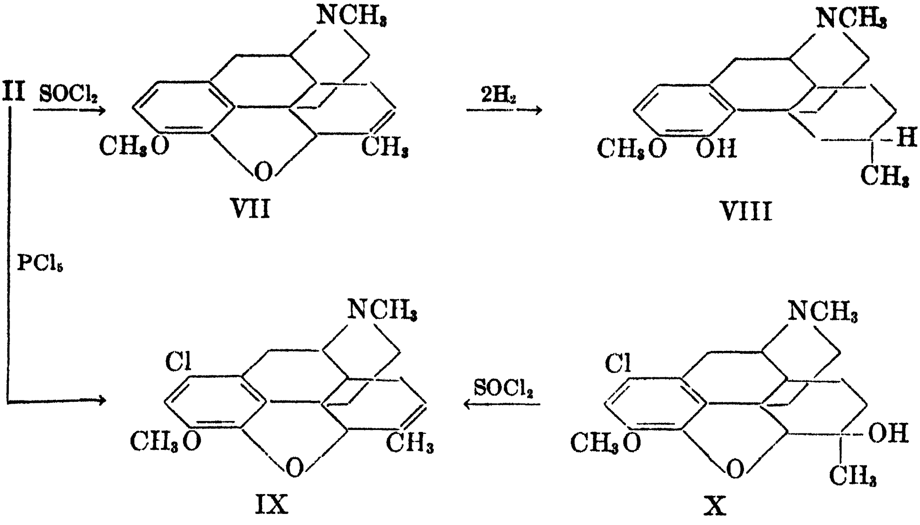
Formula Scheme A



and in position 5,6 or 6,7 (*i.e.*, ozonolysis resulted in a methyl ketone). If it were at 5,6, the compound would be a vinyl ether type and should be easily hydrolyzed by dilute acids, whereas it was found to be stable. Definite evidence for the 6,7-position was furnished by catalytic hydrogenation, which proceeded with absorption of two moles, and reductive scission of the ether bridge (VII → VIII), in the manner typical of pseudocodeine types (11). Dehydration of 6-methyldihydrocodeine with phosphorus pentoxide in toluene according to Prelog and Moor (12) gave only a small yield of the desoxy compound; most of the product was insoluble in organic media, and probably consisted of phosphoric esters.

The reaction of 6-methyldihydrocodeine with PCl_5 in chloroform (13) gave a product which contained one chlorine atom, but which had also lost the elements of water. From the known reactivity of the 1-position in the morphine series it is apparent that this must be 1-chloro-6-methyldesoxycodeine-C (IX). This assumption was verified by subjecting 1-chloro-6-methyldihydrocodeine (X) to the thionyl chloride reaction, which resulted in the same product.

Formula Scheme B



The hydrogenation of 6-methyldesoxycodeine-C with platinum oxide invariably took place in the "abnormal" manner, even under conditions that had been found to give normal reduction of the alicyclic unsaturation alone in other pseudocodeine types (11). The resulting 6-methyltetrahydrodesoxycodeine (VIII) gave a positive test for phenolic hydroxyl with diazosulfanilic acid, but like its unmethylated analog, tetrahydrodesoxycodeine (14), was practically insoluble in dilute alkali.

With palladous chloride and gum arabic buffered with sodium acetate, hydrogenation stopped at 1.3 moles, but the product was entirely phenolic, and the only isolable pure compound was the tetrahydro derivative. Continued reduction of the mixture with platinum oxide gave absorption of an additional 0.6 mole to yield pure tetrahydro derivative. It seems probable that the palladium reduction resulted in one or more dihydrodesoxycodeine types, in which the oxide ring was opened before the double bond was reduced.

In preliminary experiments, codeinone was found to react readily with methyllithium to give principally a crystalline, non-phenolic product, 6-methylcodeine, together with a small amount of phenolic material. The investigation of this series is being deferred until a reliable preparative method for codeinone is developed.

6-Methyldihydrocodeine and 6-methyldihydromorphine were tested for analgesic action by the Woolfe-Macdonald method (15). The intensity of action was not greater, but the duration of analgesia was about twice that of their unmethylated analogs. The toxicity of the methylated and unmethylated compounds was similar, but the former did not produce a Straub reaction, and apparently had much less effect on the spinal cord. Further details will be published elsewhere (N. B. Eddy).

We are indebted to C. A. Kinser and Betty Mount of this Laboratory for the microanalyses.

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes; rotations are in 95% alcohol unless otherwise specified.

Organolithium reagents. All organolithium reagents were prepared by the method of Perrino and Rapoport (16), titrated in the usual way, and stored at 0°.

6-Methyldihydrocodeine (II). In an apparatus with stirrer, condenser, and protection from moisture, 25 g. (0.084 mole) of dihydrocodeinone was added during 10 minutes to 140 ml. of 0.9 *M* methyllithium (0.126 mole) at 0°. It was stirred at room temperature for 30 minutes; Michler's ketone test showed excess methyllithium present. The solution was poured into 850 ml. of cold 2% acetic acid (this volume is necessary to prevent precipitation of alkaloid hydriodide derived from lithium iodide in the reagent), separated, and the aqueous phase washed with 100 ml. of peroxide-free ether. On slow addition of 6 *N* ammonia, the base precipitated crystalline, yield 20 g. It is appreciably soluble in water, and chloroform extraction gave an additional 5 g., total 95%. It is extremely soluble in organic media, and was purified from ether or 40% alcohol; sublimed for analysis at 130°/0.1 mm. it melted at 116°, $(\alpha)_D^{20}$ −139° (alcohol, c = 1.02).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.4; H, 7.99.
Found: C, 72.5: H, 8.05.

The *hydrochloride* was prepared with alcoholic hydrogen chloride and ether, and recrystallized from abs. alcohol-ether (1:2); m.p. 268–273°, $(\alpha)_D^{20}$ −112° (alcohol, c = 0.96)

Anal. Calc'd for $C_{19}H_{26}ClNO_3$: C, 64.8; H, 7.45.
Found: C, 64.8; H, 7.31.

The *methiodide* was prepared in and purified from methanol, m.p. 251–252°, $(\alpha)_D^{20}$ −86.3° (alcohol, c = 1.09).

Anal. Calc'd for $C_{20}H_{28}INO_3$: C, 52.5; H, 6.17.
Found: C, 52.7; H, 6.18.

The *acid oxalate,* prepared with abs. alcoholic oxalic acid and crystallized from 95% alcohol, appeared to be a hemihydrate; m.p. 240–241°, $(\alpha)_D^{20}$ −99.5° (alcohol, c = 0.97).

Anal. Calc'd for $C_{21}H_{27}NO_7 + 0.5H_2O$: C, 60.9; H, 6.81.
Found: C, 60.9; H, 6.44.

6-Methyl-6-acetyldihydrocodeine. A solution of 2 g. of 6-methyldihydrocodeine (0.006 mole) in 40 ml. of abs. ether was added slowly to 25 ml. of 0.9 *M* methyllithium (0.023 mole) (strong gas evolution). After 10 min. 2.5 ml. (0.025 mole) of acetic anhydride was added with good cooling. The resulting magma was heated to boiling, and allowed to stand 12 hours. It was decomposed with 100 ml. of 2% acetic acid, and the aqueous layer was basified with 2 *N* sodium carbonate, giving 1.5 g. (66%) of the crystalline acetyl derivative. After purification from petroleum ether (30–60°), it melted at 119–121°; sublimed at 130°/0.1 mm., m.p. 124.5–125.5°, $(\alpha)_D^{20}$ −85.1° (alcohol, c = 0.96).

Anal. Calc'd for $C_{21}H_{27}NO_4$: C, 70.5; H, 7.61.
Found: C, 70.7; H, 7.55.

Degradation. 6-Methyldihydromethylmorphimethine (III). A suspension of 15 g. of 6-methyldihydrocodeine methiodide in 100 ml. of 30% KOH was refluxed for 15 min. The alkali and resin were extracted with five 50-ml. portions of ether, from which 9 g. (83%) of pale yellow oily methine was obtained. It was extremely soluble, and could not be crystallized.

The *hydrochloride* was prepared with alcoholic hydrogen chloride and precipitated with abs. ether; it was recrystallized from abs. alcohol-ether (1:1), m.p. 241–243°, $(\alpha)_D^{20}$ −6.7° (alcohol, c = 0.41).

Anal. Calc'd for $C_{20}H_{28}ClNO_3$: C, 65.6; H, 7.71.
Found: C, 65.4; H, 7.78.

The *salicylate* was prepared in abs. alcohol; m.p. 198–200°, $(\alpha)_D^{20}$ −2.3° (alcohol, c = 0.99).

Anal. Calc'd for $C_{27}H_{33}NO_6$: C, 69.4; H, 7.11.

Found: C, 69.7; H, 7.11.

The *methiodide* was prepared in and purified from methanol; drying at 155° in a vacuum was necessary to obtain solvent-free material; m.p. 269–271°, $(\alpha)_D^{20}$ +8.1° (alcohol, c = 0.98).

Anal. Calc'd for $C_{21}H_{30}INO_3$: C, 53.5; H, 6.42.

Found: C, 53.4; H, 6.38.

6-Methyl-6-hydroxy-13-vinylhexahydromethylmorphenol (*IV*). Freshly precipitated and thoroughly washed silver oxide (from 7.7 g., 0.045 mole, of silver nitrate) and 7 g. (0.015 mole) of 6-methyldihydromethylmorphimethine methiodide in 175 ml. of water were heated on the steam-bath for several minutes, and shaken for 2 hours at room temperature. It was filtered hot, and evaporated to dryness under reduced pressure at 40°. The residue was distilled in a high vacuum onto a cold-finger; decomposition began at 90°, and was continued at 100–110° for 20 hours. The condensate was removed with 100 ml. of ether, which was washed with N HCl, N Na_2CO_3, and water. It yielded 2.6 g. (62%) of crystals, purified from petroleum ether (30–60°) and by sublimation at 100°/0.1 mm.; $(\alpha)_D^{20}$ +24.4° (alcohol, c = 0.93).

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.0; H, 7.09.

Found: C, 76.0; H, 6.99.

The acid washings yielded 300 mg. of the methine hydrochloride. The dry-ice trap in the decomposition apparatus yielded a small amount of trimethylamine; picrate m.p. 216–218° (lit. 216°).

6-Methyl-6-hydroxy-13-ethyl-5,6,7,8,9,10,13,14-octahydromethylmorphenol (*V*). Hydrogenation of 100 mg. of the N-free product (IV) in 10 ml. of methanol with 10 mg. of platinum oxide stopped at 2 moles. The product was sublimed at 100°/0.1 mm., m.p. 98–100°, $(\alpha)_D^{20}$ −29.9° (alcohol, c = 1.07).

Anal. Calc'd for $C_{18}H_{24}O_3$: C, 75.0; H, 8.39.

Found: C, 75.2; H, 8.09.

6-Methyldesoxycodeine-C (*VII*). To a solution of 45 g. (0.143 mole) of 6-methyldihydrocodeine in 270 ml. of absolute chloroform, at 0° with good stirring, was added during 30 min. 20.4 g. (0.172 mole) of thionyl chloride in 90 ml. of chloroform. The solution was refluxed for two hours and poured into 900 ml. of cold water. It was basified with ammonia, and extracted well with chloroform. The residue from the chloroform was dissolved in 250 ml. of alcohol and decolorized; dilution with 250 ml. of hot water gave 23.5 g. of product, and 4 g. more on further dilution (65% yield). It was purified from alcohol, m.p. 172–174°, sublimed at 120°/0.2 mm., m.p. 173–174°, $(\alpha)_D^{20}$ −242° (alcohol, c = 1.07); diazosulfanilic acid test negative, $KMnO_4$ in acetone slowly decolorized.

Anal. Calc'd for $C_{19}H_{23}NO_2$: C, 76.7; H, 7.80.

Found: C, 76.9; H, 7.71.

The *hydrochloride*, from abs. ethanol-ether, melted at 262–263°, $(\alpha)_D^{20}$ −192° (alcohol, c = 1.02).

Anal. Calc'd for $C_{19}H_{24}ClNO_2$: C, 68.3; H, 7.25.

Found: C, 67.9; H, 7.37.

The *methiodide* crystallized from methanol, m.p. 280–281°, $(\alpha)_D^{20}$ −149° (alcohol, c = 1.00).

Anal. Calc'd for $C_{20}H_{26}INO_2$: C, 54.7; H, 5.97.

Found: C, 54.8; H, 6.04.

The desoxy compound was also obtained by the action of phosphorus pentoxide in toluene, but the yield was only 10%. 6-Methyldesoxycodeine-C was recovered unchanged from normal HCl after 15 min. at 100°.

Ozonolysis. Oxygen containing 2.7% ozone was passed through a solution of 1.7 millimoles of 6-methyldesoxycodeine-C in normal HCl at the rate of 12 l. per hour. In 30 min. 1.9 millimoles was absorbed. The methone test for formaldehyde was negative, but with iodine and alkali a precipitate of iodoform, m.p. 119–120° was obtained.

6-Methyltetrahydrodesoxycodeine (*VIII*). A solution of 3 g. of 6-methyldesoxycodeine-C in 150 ml. of 5% sulfuric acid with 150 mg. of platinum oxide absorbed 2.0 moles of hydrogen in 1.5 hours. The product was precipitated with solid potassium carbonate and recrystallized from acetone, yield 66%; sublimed at 125°/0.2 mm. it melted at 157.5–158.5°, $(\alpha)_D^{20}$ −4.5° (alcohol, c = 0.61).

Anal. Calc'd for $C_{19}H_{27}NO_2$: C, 75.7; H, 9.03.
Found: C, 75.8; H, 9.08.

The *hydrochloride* crystallized from abs. alcohol-ether, m.p. 254–255°, $(\alpha)_D^{20}$ +8.0° (alcohol, c = 0.81).

Anal. Calc'd for $C_{19}H_{28}ClNO_2$: C, 67.5; H, 8.35.
Found: C, 67.8; H, 8.54.

The *acid oxalate*, from alcohol-ether, had the m.p. 171–172°, $(\alpha)_D^{20}$ +4.8° (alcohol c = 0.68).

Anal. Calc'd for $C_{21}H_{29}NO_6$: C, 64.4; H, 7.47.
Found: C, 64.5; H, 7.57.

The *methiodide*, from methanol-ether, melted at 265–266°; $(\alpha)_D^{20}$ +6.4° (alcohol, c = 0.47).

Anal. Calc'd for $C_{20}H_{30}INO_2$: C, 54.2; H, 6 82.
Found: C, 54.3; H, 6.78.

Hydrogenation of 4.4 g. of 6-methyldesoxycodeine-C in 120 ml. of methanol with 2.2 g. of sodium acetate, 40 mg. of gum arabic, and 4.5 ml. of 1% palladous chloride stopped completely at 1.3 moles of hydrogen. Fractionation gave the tetrahydro compound as the only pure product; the phenolic residues absorbed 0.6 mole of hydrogen with platinum oxide to yield an additional quantity.

1-Chloro-6-methyldesoxycodeine-C (*IX*). To a solution of 6.5 g. (0.031 mole) of phosphorus pentachloride in 25 ml. of abs. chloroform at 0° was added 5.0 g. (0.016 mole) of 6-methyldihydrocodeine in small portions over 10 min. The solution was refluxed for 4 hours, 500 ml. of water was added, and the chloroform removed at reduced pressure. After filtration from a little insoluble material, the solution was basified and extracted with ether, which yielded 4.4 g. of syrupy residue. Digestion with abs. ether gave 1.5 g. of crystals, purified from abs. alcohol and sublimed at 150°/0.1 mm.; m.p. 171–172°, $(\alpha)_D^{20}$ −226° (alcohol, c = 1.12). It decolorized $KMnO_4$ in acetone at 20°.

Anal. Calc'd for $C_{19}H_{22}ClNO_2$: C, 68.8; H, 6.68; Cl, 10.7.
Found: C, 68.9, 68.6; H, 6.63, 6.45; Cl, 10.4.

The same compound was obtained when the base from 2.0 g. of 1-chloro-6-methyldihydrocodeine perchlorate in 15 ml. of abs. chloroform with 0.63 g. of thionyl chloride was refluxed for two hours. The product, purified as above, 0.5 g., melted at 171–172°, no depression in mixture, and had $(\alpha)_D^{20}$ −227° (alcohol, c = 1.14).

1-Chloro-6-methyldihydrocodeine (X). This was prepared essentially like the unchlorinated analog, but was obtained from ether extraction as an oil. It was dissolved in abs. ethanol and converted to the *perchlorate* with normal alcoholic $HClO_4$, yield 76%. The salt was purified from abs. ethanol, m.p. 238–239°, $(\alpha)_D^{20}$ −81.4° (alcohol, c = 0.96).

Anal. Calc'd for $C_{19}H_{25}Cl_2NO_7 + 0.5\ H_2O$: C, 49.7; H, 5.71.
Found: C, 49.4; H, 5.61.

The *hydriodide* was prepared with 15% alcoholic hydriodic acid, and purified from abs. alcohol; m.p. 260–262°, $(\alpha)_D^{20}$ −73.6° (alcohol, c = 0.94).

Anal. Calc'd for $C_{19}H_{25}ClINO_3$: C, 47.8; H, 5.27.
Found: C, 47.6; H, 5 59.

1-Bromo-6-methyldihydrocodeine. This compound, prepared from 1-bromodihydrocodeinone like the chloro analog, was obtained in 86% yield as an amorphous solid, m.p. 60–70°, exceedingly soluble in organic media. The *hydrochloride* was also very soluble, and hygroscopic. The *hydriodide* was prepared with 10% aqueous hydriodic acid, and purified from water, m.p. 248–249°, $(\alpha)_D^{20}$ −64.6° (alcohol, c = 1.05).

Anal. Calc'd for $C_{19}H_{25}BrINO_3$: C, 43.7; H, 4.83.
Found: C, 43.3; H, 5.06.

The *methiodide*, from methanol-ether, melted at 235–237°, $(\alpha)_D^{20}$ −73.1° (alcohol, c = 1.20).

Anal. Calc'd for $C_{20}H_{27}BrINO_3$: C, 44.8; H, 5.08.
Found: C, 45.1; H, 5.05.

6-Methyldihydromorphine (VI). This was prepared like the codeine analog from 12 g. (0.042 mole) of dihydromorphinone and 120 ml. of 0.9 *M* methyllithium (0.11 mole). It precipitated crystalline on addition of solid potassium carbonate to the HCl solution; chloroform extracted an additional amount; after recrystallization from acetone 8.7 g. was obtained, 69%. It sublimed at 150°/0.1 mm., m.p. 209–211°, $(\alpha)_D^{20}$ −147° (alcohol, $c = 1.02$). It adsorbed about 1% moisture avidly.

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.69.
Found: C, 71.8; H, 7.69.

The *hydrochloride* crystallized from alcohol-ether, m.p. 308–309°, $(\alpha)_D^{20}$ −121° (alcohol, $c = 1.04$).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: C, 64.0; H, 7.16.
Found: C, 63.8; H, 6.94.

The *methiodide* crystallized from methanol, m.p. 277–278°, $(\alpha)_D^{20}$ −86.8° (alcohol, $c = 0.53$). It turned yellow quite rapidly.

Anal. Calc'd for $C_{19}H_{26}INO_3$: C, 51.5; H, 5.91.
Found: C, 51.7; H, 6.15.

The base was allowed to stand with excess ethereal diazomethane and methanol for two days. The product was 6-methyldihydrocodeine, m.p. 112–113°, no depression in mixture.

6-Ethyldihydrocodeine. The petroleum ether (b.p. 28–38°) was evaporated under reduced pressure from 380 ml. of 0.27 *M* ethyllithium (0.103 mole) to a volume of about 10 ml., and 150 ml. of abs. ether was added. The reaction with 10 g. (0.034 mole) of dihydrocodeinone was carried out as with the methyl analog, and after decomposition with HCl, basifying with NaOH, and ether extraction, an oily residue was obtained from which 0.5 g. of dihydrocodeinone was isolated; the ethyl derivative could not be crystallized. Most salts were oily or very soluble.

The *picrate* was prepared with alcoholic picric acid and purified from 75% alcohol, m.p. 217–219°, $(\alpha)_D^{20}$ −73.0° (75% alcohol, $c = 0.60$).

Anal. Calc'd for $C_{26}H_{30}N_4O_{10}$: C, 55.9; H, 5.41.
Found: C, 56.3; H, 5.64.

The *methiodide*, from methanol-ether, was purified from abs. alcohol, m.p. 238–240°, $(\alpha)_D^{20}$ −82.0° (alcohol, $c = 1.11$).

Anal. Calc'd for $C_{21}H_{30}INO_3$: C, 53.5; H, 6.42.
Found: C, 53.4; H, 6.43.

6-n-Amyldihydrocodeine. The reaction of dihydrocodeinone (5 g.) with *n*-amyllithium was carried out as for the ethyl compound. The product was 5.8 g. of oil, from which *N* alcoholic $HClO_4$ precipitated 0.6 g. (9%) of dihydrocodeinone perchlorate. The regenerated amyl derivative did not crystallize or give crystalline salts. Repeated distillation of the base at 140°/0.2 mm. gave a viscous, faintly yellow oil, having $(\alpha)_D^{20}$ −108° (alcohol, $c = 0.88$).

Anal. Calc'd for $C_{23}H_{33}NO_3$: C, 74.5; H, 8.95.
Found: C, 73.8; 73.7; H, 9.15, 8.90.

6-Phenyldihydrocodeine. To 60 ml. of 0.84 *M* ethereal phenyllithium (0.05 mole) was added, at 0°, 10 g. (0.033 mole) of dihydrocodeinone. After 10 min. the mixture was poured into 500 ml. of cold 3% acetic acid. The acid layer was washed with ether, basified, and extracted with ether, from which a liquid product was obtained. This was dissolved in 300 ml. of alcohol and treated with 50 ml. of *N* alcoholic perchloric acid, yield of crystalline salt 13.7 g. (86%). The salt was recrystallized four times from alcohol; the base liberated did not crystallize, and was distilled at 130°/0.1 mm. yielding an amorphous solid, m.p. 62–72°, $(\alpha)_D^{20}$ −155° (alcohol, $c = 1.08$).

Anal. Calc'd for $C_{24}H_{27}NO_3$: C, 76.4; H, 7.21.
Found: C, 76.2; H, 7.11.

The *perchlorate* melted at 246–248° and had $(\alpha)_D^{20}$ −126° (50% alcohol, $c = 0.404$).

Anal. Calc'd for $C_{24}H_{28}ClNO_7$: C, 60.3; H, 5.91.
Found: C, 60.4; H, 5.91.

The *hydrochloride* was prepared in 2.5 *N* aqueous hydrochloric acid and recrystallized from 1:1 abs. alcohol-ether; m.p. 190–191°, $(\alpha)_D^{20}$ −131° (alcohol, $c = 1.04$).

Anal. Calc'd for $C_{24}H_{28}ClNO_3$: C, 69.6; H, 6.82.
Found: C, 69.5, H, 7.18.

The *acid oxalate* was prepared with alcoholic oxalic acid and ether, and recrystallized from alcohol-ether; it retained one-half molecule of ethanol after vacuum-drying at 100°; m.p. 126–127°, $(\alpha)_D^{20}$ −117° (alcohol, $c = 1.00$).

Anal. Calc'd for $C_{26}H_{29}NO_7 + 0.5\ C_2H_6O$: C, 66.1; H, 6.58.
Found: C, 66.2; H, 6.84.

SUMMARY

The reaction of some ketones of the morphine series with organolithium compounds is described. In contrast to RMgX, the reagent adds at the carbonyl to give 6-substituted tertiary alcohols.

Degradation of 6-methyldihydrocodeine to a nitrogen-free product is described.

Thionyl chloride dehydrates 6-methyldihydrocodeine to 6-methyldesoxycodeine-C, whereas phosphorus pentachloride chlorinates at the 1-position in addition.

6-Methyldesoxycodeine-C undergoes reduction to a phenolic tetrahydro derivative, like its unmethylated analog.

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[Contribution from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, No. 1090]

PHOSPHORUS OXYBROMIDE AS A BROMINATING AGENT. BROMOPYRIMIDINES[1]

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Received September 16, 1946

The introduction of bromine into the 4 or 6 position of the pyrimidine nucleus has been reported in only one case, that of the preparation of 2,4,5,6-tetrabromopyrimidine, by the reaction of a mixture of phosphorus pentabromide and phosphorus oxychloride with 5-hydroxybarbituric acid (1). On the other hand pyrimidines with chlorine in these positions are readily prepared by the use of phosphorus oxychloride (2).

While attempting to synthesize analogs of sulfadiazine brominated in the pyrimidine ring, we found that the required bromopyrimidines could be prepared by the action of phosphorus oxybromide on the corresponding hydroxypyrimidines. Direct fusion of the reactants led to the formation of 2,4,6-tribromopyrimidine, 2-amino-4-bromopyrimidine, 2-amino-4,6-dibromopyrimidine, and 2-amino-4-bromo-6-methylpyrimidine, in moderate yields; a good yield of 2-(*p*-nitrobenzenesulfonamido)-4-bromo-6-methylpyrimidine was obtained when the reaction was carried out employing toluene as a diluent. The desirable physical properties of phosphorus oxybromide and its ease of handling suggest that it might find more general use as a brominating agent.

EXPERIMENTAL[3]

Phosphorus oxybromide. This material was prepared by the method of Berger (3), and was then distilled, b.p. 89–90°/20 mm. It was a colorless, crystalline solid, which could be preserved indefinitely in a desiccator. It was convenient to melt the compound when weighing a portion of it for use.

2,4,6-Tribromopyrimidine. Ten grams of barbituric acid and 143 grams of phosphorus oxybromide were heated at 150–160° for five and one-half hours; the mixture was then cooled and added slowly to an ice-ether mixture which had been cooled to −10°. The precipitate was collected, extracted with ether, and the combined ethereal extracts dried. The ether was removed and the material which remained was distilled, giving 15 grams (61%) of product, b.p. 124°/5 mm., m.p. 113–115°.

Anal. Calc'd for $C_4HBr_3N_2$: C, 15.16; H, 0.31; N, 8.84.
Found: C, 15.34; H, 0.41; N, 8.61.

2-Amino-4-bromopyrimidine.[4] Four grams of isocytosine (4) and 10 g. of phosphorus oxybromide were mixed and heated for two hours, while the temperature was slowly raised from 80° to 135°, and finally held at the higher temperature. The melt was decomposed with ice, the solution was brought to *p*H 12, and the product, 1.0 g. (16%), filtered off. It was purified by recrystallization from water, and an analytical sample was prepared by sublimation at 110–120° and atmospheric pressure. The product had no melting point, but decomposed slowly when heated above 130°.

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[1] The work described in this paper was carried out under contracts, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the California Institute of Technology. Work under the contracts was carried out under the direction of Drs. E. R. Buchman and J. B. Koepfli, respectively.

[2] Present address: duPont Experimental Station, Wilmington, Delaware.

[3] All melting points reported in this paper are corrected for exposed stem. The microanalyses were carried out by Dr. Gertrude Oppenheimer and her staff, of this institute.

[4] This reaction was carried out by Mr. John T. Maynard.

Anal. Calc'd for $C_4H_4BrN_3$: C, 27.61; H, 2.32.
Found: C, 27.28; H, 2.31.

2-Amino-4,6-dibromopyrimidine. A mixture of 1.70 g. of 2-amino-4,6-dihydroxypyrimidine (5) and 6.8 g. of phosphorus oxybromide was heated to 135°, initiating a vigorous reaction, with evolution of hydrogen bromide. When the reaction had subsided the melt was poured over ice, and the solid product was filtered off and recrystallized from ethanol, giving 1.10 g. (32%) of material which melted at 180–186° after sintering from 155°. An analytical sample was sublimed *in vacuo*, and melted at 189.5–192.5°.

Anal. Calc'd for $C_4H_3Br_2N_3$: C, 19.00; H, 1.19.
Found: C, 19.11; H, 1.42.

2-Amino-4-bromo-6-methylpyrimidine. Thirty grams of crude 2-amino-4-hydroxy-6-methylpyrimidine (6) was treated with 135 g. of molten phosphorus oxybromide, whereupon an immediate reaction ensued. After forty-five minutes at 135° the mixture was cooled and added to 600 g. of ice. To the resulting aqueous solution 15 *N* ammonia was added slowly with cooling. The supernate was decanted from a red gummy precipitate which came down while the solution was still strongly acid, and the crude product was precipitated by adding an excess of ammonia. It was partially purified by reprecipitation from acid solution. The crude solid weighed 22 g., from which 10–15 g. of pure product, m.p. 153°, could be isolated by recrystallization from isopropyl ether or from acetone and water.

Anal. Calc'd for $C_5H_6BrN_3$: C, 31.94; H, 3.22; N, 22.35.
Found: C, 31.84; H, 2.98; N, 22.23.

2-(p-Nitrobenzenesulfonamido)-4-bromo-6-methylpyrimidine. Fifteen grams of phosphorus oxybromide was dissolved in 60 ml. of dry toluene, and 6.5 g. of 2-(*p*-nitrobenzenesulfonamido)-4-hydroxy-6-methylpyrimidine (7) was added. The resulting suspension was refluxed for seven hours, cooled, and shaken with ice to decompose unreacted oxybromide. The product was recovered by filtration, and recrystallized from 250 ml. of ethanol and 200 ml. of water to give 6.1 g. (78%) of thin, colorless bars, m.p. 210.5–212.5° (dec.).

Anal. Calc'd for $C_{11}H_9BrN_4O_4$: C, 35.40; H, 2.43; N 15.02.
Found: C, 35.11; H, 2.39; N, 15.12.

SUMMARY

1. The use of phosphorus oxybromide as a reagent for the bromination of hydroxypyrimidines is reported.

2. A number of new bromopyrimidines, with bromine in the 2, 4, and 6-positions are reported.

PASADENA, CALIF.

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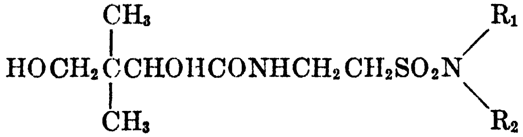
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1094]

THE SYNTHESIS OF POTENTIAL ANTIMALARIALS. THE PREPARATION OF METHYLATED AMIDES OF TAURINE AND THEIR PANTOYL DERIVATIVES[1]

J. F. MEAD[2] AND J. B. KOEPFLI

Received September 16, 1946

During an investigation of compounds related to pantoyltaurine as potential antimalarials, a number of derivatives of pantoyltaurylamide (I) were prepared (1). In each instance these compounds were characterized by a free acidic hydrogen on the sulfonamide nitrogen. In order to investigate the effect of this hydrogen on the antimalarial properties of the drugs, it was thought best to substitute for it the methyl group and to compare the activity of compounds possessing one, two, and no acidic hydrogens. For this purpose, the methylamide and the dimethylamide derivatives of taurine were prepared and condensed with pantolactone to give crude preparations of pantoyltaurine methylamide (II) and dimethylamide (III). The antimalarial activities of these latter compounds are comparable to that of pantoyltaurylamide (SN 3279) and are reported elsewhere.[3, 4]



$$\mathrm{HOCH_2\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}CHOHCONHCH_2CH_2SO_2N}\begin{matrix}\diagup R_1\\ \\ \diagdown R_2\end{matrix}$$

I, $R_1 = R_2 = H$; II, $R_1 = H$, $R_2 = CH_3$; III, $R_1 = R_2 = CH_3$

In the preparation of the monomethyl amide, an interesting reaction was observed which lead to the elimination of two steps in the synthesis. In the reaction of methylamine with β-phthalimidoethanesulfonyl chloride, the methylamine not only replaced the chlorine of the acid chloride, but also removed the phthalyl group with the formation of N-methylphthalimide. Thus the usual hydrolysis with hydrazine hydrate and hydrochloric acid (2) was eliminated, and the desired taurine methylamide was obtained directly from the reaction mixture. This reaction is illustrated below:

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[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology.

[2] Present Address: Department of Chemistry, Occidental College, Los Angeles.

[3] The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activity will be tabulated in a monograph entitled "Antimalarial Drugs, 1941–1945", F. Y. Wiselogle, editor, in press.

[4] While this paper was in press, the authors learned by private communication that some of the compounds described had also been prepared by R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, and R. O Roblin, Jr.; *J. Am. Chem. Soc.*, in press. Footnote added to proof Feb. 25, 1947.

$$C_6H_4(CO)_2{=}NCH_2CH_2SO_2Cl + 2\ CH_3NH_2 \rightarrow$$

$$C_6H_4(CO)_2{=}NCH_3 + NH_2CH_2CH_2SO_2NHCH_3$$

An instance in which methylamine unexpectedly acted in an analogous manner has been reported by Ristenpart (3), who, in an attempt to prepare β-phthalimidoethylmethylamine from β-phthalimidoethylbromide and methylamine, obtained N-methylphthalimide in 85% yield. The possibility of the use of methylamine as a general reagent for this type of reaction is being investigated further.

EXPERIMENTAL[5]

β-Phthalimido-N-dimethylethanesulfonamide. Fifty-four grams of β-phthalimidoethanesulfonyl chloride was dissolved in 600 ml. of warm benzene and dry dimethylamine was passed into the hot solution until the precipitation of dimethylamine hydrochloride was complete. The benzene solution was decanted and evaporated to dryness, and the residue was dried over sulfuric acid. The resulting oil solidified when treated with water and a little hydrochloric acid. The solid thus formed was filtered and dried to give 43 g. of product of m.p. 153–156°. A sample crystallized from water as long colorless needles, m.p. 154–156°.

Anal. Calc'd for $C_{12}H_{14}N_2O_4S$: C, 51.0; H, 5.0; N, 9.9.
Found: C, 51.0; H, 4.8; N, 9.6.

Taurine dimethylamide hydrochloride. Forty grams of the above prepared phthalyl compound was dissolved in 300 ml. of absolute ethanol and treated with 9 g. of hydrazine hydrate (2). By working up the reaction mixture in the usual manner (1, 4), there was obtained 20 g. of crystalline hydrochloride of m.p. 141–143°. A sample crystallized from isopropyl alcohol for analysis melted at 144–146°.

Anal. Calc'd for $C_4H_{13}ClN_2O_2S$: C, 25.5; H, 6.9.
Found: C, 25.9; H, 7.0.

Taurine dimethylamide. To 9.5 g. of the above prepared hydrochloride dissolved in a small amount of water was added the theoretical amount of sodium bicarbonate. The water was evaporated *in vacuo*, and the residue was dried thoroughly and extracted with a small amount of absolute ethanol. On evaporation of the solvent, there was obtained 6.9 g. of light green oil which did not solidify above 0°. For purification, it was distilled at 110–115°/50–60μ.

Anal. Calc'd for $C_4H_{12}N_2O_2S$: C, 31.6; H, 8.0.
Found: C, 31.6; H, 8.0.

(+)-Pantoyltaurine dimethylamide (II) (SN 7468).[3] A mixture of 5.4 g. of taurine dimethylamide and 4.8 g. of *l*-pantolactone was heated for two hours at 100°. The resulting liquid was cooled, washed thoroughly with ether, and dried under high vacuum to give 10 g. of a viscous oil which could not be induced to crystallize and could not be obtained pure enough to give reproducible analyses; $[\alpha]_D^{25}$ +19.2° (0.1206 g. in 5.00 ml. of water).

Taurine methylamide hydrochloride. Twenty-seven grams of β-phthalimidoethanesulfonyl chloride was dissolved in 250 ml. of hot benzene, and a rapid stream of dry methylamine was passed into the hot solution. After fifteen minutes, the cloudy solution was placed on the steam-bath, and the methylamine addition continued for one-half hour. The benzene solution was decanted from the gummy precipitate which had formed and the precipitate was dried thoroughly to remove excess methylamine, dissolved in a little water, and treated with sodium bicarbonate. The basic solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in hot ethanol, acidified with concentrated hydrochloric acid, and allowed to cool. The crystals which precipitated on cooling were filtered and dried to give 6.2 g. of product m.p. 166–169°, pure enough for the next reaction. On recrystallization from ethanol, it was obtained as colorless platelets, m.p. 169–170°.

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[5] All melting points have been corrected for exposed stem. The microanalyses reported have been carried out by Dr. Gertrude Oppenheimer and Mr. G. A. Swinehart.

Anal. Calc'd for $C_3H_{11}ClN_2O_2S$: C, 20.6; H, 6.4; N, 16.3.
Found: C, 21.0; H, 6.4; N, 16.3.

Taurine methylamide. The taurine methylamide hydrochloride obtained above was dissolved in a small amount of water, and the theoretical amount of sodium bicarbonate was added. The solution, after filtration, was evaporated to dryness, and the dried residue extracted with absolute ethanol. After evaporation of the solvent and thorough drying of the residue, an oily solid was obtained. This was purified by dissolving it in isopropyl alcohol, filtering the solution, and precipitating the product as a colorless crystalline solid, m.p. 69–70°, with petroleum ether (30–60°). A portion of the product was recrystallized from a mixture of isopropyl alcohol and isopropyl ether giving clusters of colorless needles, m.p. 71–72°.

Anal. Calc'd for $C_3H_{10}N_2O_2S$: C, 26.1; H, 7.3; N, 20.3.
Found: C, 26.0; H, 7.0; N, 20.3.

(+)-*Pantoyltaurine methylamide* (*II*) (*SN 7469*). The condensation with pantolactone was carried out as described above with 6.2 g. of the methylamide and 6.0 g. of *l*-pantolactone. The product was a viscous oil which could not be induced to crystallize and could not be obtained sufficiently pure to give reproducible analyses; $[\alpha]_D^{23}$ +17.0° (0.0294 g. in 2.00 g. water).

SUMMARY

The preparation is described of taurine methylamide and dimethylamide and their pantoyl derivatives.

The metathesis of β-phthalimido-N-methylethanesulfonamide by methylamine is discussed.

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[FROM THE LABORATORIES OF HYNSON, WESTCOTT, AND DUNNING, INC.]

SOME HIGHLY HALOGENATED PHENOLIC ETHERS AS FUNGISTATIC COMPOUNDS

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The fungistatic activity of the highly halogenated phenols is well known and has been the basis for considerable investigation. For use in the treatment of human infections, solutions of these phenols are too toxic for continued use, being absorbed through the skin. For this reason, these compounds are used mainly as preservatives, as in fungus-resisting paints, mildew-proofing chemicals, and the like (1).

It was thought that certain ethers of these phenols might retain at least some of the fungistatic activity of the parent substances, and at the same time possess lower toxicities. The phenols used were 2,4,6-trichloro-, 2,3,4,6-tetrachloro-, 2,3,4,5,6-pentachloro-, and 2,4,6-tribromo-phenol. Six representative ethers of each phenol were prepared. Since three of the compounds were not obtained sufficiently pure to be tested, results for only twenty-one are given in this report (see Table I). Twelve of the compounds have not been previously described, although the methods of preparation are known.

From the results of the table, it will be seen that in all cases there was a considerable drop in fungistatic ability against *Trichophyton mentagraphtes* #640 of the ether compared to that of the parent phenol. It is interesting to note that the derivatives of tribromophenol possessed only slight activity, although this phenol was apparently the best compound tested. On the other hand, of the ethers derived from the chlorinated phenols, there were several which were appreciably active. The best series was the phenoxyethanols, and even in dilutions of 1:2000, the highest dilution at which the parent phenols showed activity, tetrachlorophenoxyethanol and pentachlorophenoxyethanol were measurably active.

While no definite conclusions may be drawn concerning the relationship between structure and fungistatic strength in this series, it appears that certain generalizations may be made. A halogen atom in the aliphatic portion of the ether produces compounds which have no value as fungistats. Further, the greater the amount of halogen, the lower the activity shown by the compounds (bromoethyl ethers *vs.* dibromopropyl ethers). Alkyl ethers, either saturated or unsaturated (isopropyl and allyl, respectively) appear to be equally active. This activity disappears in the first 10^{-1} dilution. Into this same category fall the phenoxyacetic acids, of current interest as weed killers.

In attempting to evaluate these results, the same test for fungistatic activity was run on propionic acid-sodium propionate, a product which has been used clinically with success. The high degree of activity of this preparation disappears completely on 10^{-1} dilution. Therefore, on the basis of the test employed, several of the ethers prepared in this study appear promising.

TABLE I
HALOGENATED PHENOLS AND THEIR ETHERS

NAME	EMPIRICAL FORMULA	M.P., °C	HALOGEN ANALYSIS, %	FUNGISTATIC ACTIVITY IN MM. OF INHIBITION AGAINST *Trichophyton mentagraphytes* # 640			
				5%	0.5%	0.05%	0.005%
2,4,6-Trichlorophenol	$C_6H_3Cl_3O$	67	—	Comp.[a]	Comp.	9	0
2,3,4,6-Tetrachlorophenol	$C_6H_2Cl_4O$	69	—	Comp.	Comp.	10	
2,3,4,5,6-Pentachlorophenol	C_6HCl_5O	190	—	15	13	5	0
2,4,6-Tribromophenol	$C_6H_3Br_3O$	94	—	Comp.	Comp.	5	0
2-(Trichlorophenoxy)-ethanol (2)	$C_8H_7Cl_3O_2$	77	—	Comp.	5	0	0
2-(Tetrachlorophenoxy)-ethanol	$C_8H_6Cl_4O_2$	51–53	Calc'd 51.41 Found 51.84	25	17	±	0
2-(Pentachlorophenoxy)-ethanol	$C_8H_5Cl_5O_2$	92–94	Calc'd 57.14 Found 57.45	11	10	9	0
2-(Tribromophenoxy)-ethanol (2)	$C_8H_7Br_3O_2$	116	—	5	±	0	
Trichlorophenoxyacetic acid (3)	$C_8H_5Cl_3O_3$	179–181	—	Comp.	0	0	
Tetrachlorophenoxyacetic acid	$C_8H_4Cl_4O_3$	170–172	Calc'd 49.28 Found 49.47	8	±	0	
Pentachlorophenoxyacetic acid	$C_8H_3Cl_5O_3$	187–189	Calc'd 54.66 Found 54.32	10	2	0	
Tribromophenoxyacetic acid (3)	$C_8H_5Br_3O_3$	200	—	3	0	0	
Trichlorophenoxyethyl bromide (4)	$C_8H_6BrCl_3O$	47–48	—	2	±	0	
Tetrachlorophenoxyethyl bromide	$C_8H_5BrCl_4O$	43–45	Calc'd 65.55 Found 65.19	2	±	0	
Pentachlorophenoxyethyl bromide	$C_8H_4BrCl_5O$	77–79	Calc'd 69.00 Found 68.28	5[b]	0	0	
Tribromophenoxyethyl bromide	$C_8H_6Br_4O$	84–86	Calc'd 73.03 Found 73.5	0	0	0	
Allyl trichlorophenyl ether (5)	$C_9H_7Cl_3O$	43–45	Calc'd 46.8 Found 46.61	Comp.	±	0	
Allyl tetrachlorophenyl ether	$C_9H_6Cl_4O$	B.P. 150/ 6 mm.	Calc'd 52.3 Found 52.5	Comp.	0	0	
Allyl pentachlorophenyl ether	$C_9H_5Cl_5O$	101–103	Calc'd 57.84 Found 58.02	3	±	0	

[a] "Comp." indicates complete inhibition on a 90-mm. petri dish.

[b] Initial solution strength was 2.5%.

[c] Initial solution strength was 20%, and dilutions were 10^{-1}, to 2% and 0.2%.

The analyses reported in this table were run by Mr. A. E. Stickels.

TABLE I—*Continued*

NAME	EMPIRICAL FORMULA	M.P., °C	HALOGEN ANALYSIS, %	FUNGISTATIC ACTIVITY IN MM. OF INHIBITION AGAINST *Trichophyton mentagrophytes* # 640			
				5%	0.5%	0.05%	0.005%
Allyl tribromophenyl ether	$C_9H_7Br_3O$	77	—	5	0	0	
β,γ-Dibromopropyl trichlorophenyl ether	$C_9H_8Br_2Cl_3O$	54–56	Calc'd 67.34 Found 67.19	0	0	0	
β,γ-Dibromopropyl pentachlorophenyl ether	$C_9H_6Br_2Cl_5O$	122–124	Calc'd 72.23 Found 73.1	0[b]	0	0	
β,γ-Dibromopropyl tribromophenyl ether	$C_9H_8Br_5O$	42.5–43.5	—	0	0	0	
Isopropyl pentachlorophenyl ether	$C_9H_7Cl_5O$	44.46	Calc'd 57.49 Found 57.85	6	0	0	
Isopropyl tribromophenyl ether (6)	$C_9H_9Br_3O$	40	—	6	±	0	
Propionic acid-sodium propionate	—	—	—	Comp.[c]	0	0	

TABLE II

COMPARATIVE TOXICITY* OF HALOGENATED PHENOLS AND THEIR ETHERS

	M.L.D. PER KILOGRAM
Pentachlorophenol	75 mgm.
Pentachlorophenoxyacetic acid	125 "
Pentachlorophenoxyethanol	250 "
Isopropylpentachlorophenyl ether	300 "
Tetrachlorophenol	250 "
Tetrachlorophenoxyethanol	250 "
Allyl tetrachlorophenyl ether	375 "
Trichlorophenol	250 "
Trichlorophenoxyethanol	250 "
Allyl trichlorophenyl ether	300 "
Tribromophenol	375 "
Sodium propionate-propionic acid	1000 "

* All toxicities are based on intraperitoneal injection in 20 gm. mice.

Toxicities for mice on a number of the compounds in the series were determined and it can be seen that as far as a single dose is concerned, the phenolic ethers are generally less toxic than the parent phenols (see Table II). Because of its considerable fungistatic activity, the lower toxicity of pentachlorophenoxyethanol compared to pentachlorophenol is of particular interest.

On the basis of the preliminary work reported here, it may be seen that several of the new compounds have favorable therapeutic indices. The phenoxyethanols in particular constitute a series of compounds which show definite promise as fungistatic substances.

EXPERIMENTAL

Technique of fungistatic test. A slight modification of the cup plate test of Emmons (7) was employed. Six Sabouraud Dextrose Agar (BBL) plates were inoculated with *Trichophyton mentagraphytes* #640 (supplied by Dr. E. L. Keeney of the Department of Medicine, Johns Hopkins University) and allowed to grow for fourteen days at 27°. The fungus mats were then scraped from the agar surface and placed in a flask containing glass beads and a small volume of saline. After shaking vigorously for ten to fifteen minutes, the beads and mycelium filaments were strained from the spore suspension, using several thicknesses of cheese-cloth.

The spores were counted with a hemocytometer and the suspension so diluted as to contain 10,000,000 spores of the trichophyton per millimeter. Physiological saline (0.85%) was used as the diluent and aseptic technique was observed throughout the preparation of the spore suspension. This suspension can be stored successfully in the refrigerator at 4–10° in screw-cap bottles for several months.

Pour-plates for the test proper were prepared by adding 0.5 cc. of the spore suspension to 22–24 cc. of Sabouraud Dextrose Agar, previously cooled to 42°. After the plates were hardened in a refrigerator for fifteen minutes, holes were cut in the center of the agar with a sterile brass cork borer, 15 mm in diameter. It is unnecessary to seal the bottom of the hole after the plug has been removed.

One-tenth cc. of the solution or suspension to be tested was then pipetted into the hole. The plates were incubated for four days at 27°. Inhibition was measured in millimeters from the edge of the cup to the nearest place that the fungus growth appears.

Polyethylene glycol-400 was used as a vehicle and diluent for the compounds in this investigation. Dilutions of the sodium propionate-propionic acid were also made with this solvent.

Preparation of phenoxyethanols. The general procedure involved refluxing for three hours 0.1 mole of phenol in 80 cc. of water containing 4.3 g. NaOH with 0.2 mole of ethylene chlorohydrin. The unchanged phenol was washed out with 10% NaOH and the product crystallized from ethanol or dilute ethanol.

Preparation of phenoxyacetic acids. One-tenth mole of phenol was refluxed for three hours with 0.1 mole of chloracetic acid in 80 cc. of H_2O containing 0.2 mole of NaOH. On cooling, the product crystallized and was recrystallized from ethanol or benzene.

Preparation of phenoxyethyl bromides. The procedure used was that of Jacobs and Heidelberger (4).

Preparation of the allyl phenyl ethers. One-tenth mole of phenol in 40 cc. of ethanol containing 0.1 mole of NaOH was refluxed and 0.15 mole of allyl chloride added dropwise over a period of ten minutes. Refluxing was continued for one hour and the reaction mixture added to two volumes of water. The product was water-insoluble. With the exception of allyl tetrachlorophenyl ether, which was distilled, the products were recrystallized from ethanol.

Preparation of the dibromopropyl phenyl ethers. The calculated quantity of bromine in $CHCl_3$ was added to a solution of the allyl ether in $CHCl_3$. The solvent was distilled off and the product recrystallized from ethanol.

Preparation of the isopropyl ethers. One-tenth mole of phenol in 60 cc. of ethanol containing 0.1 mole of KOH was heated in a sealed tube with 0.2 mole of isopropyl chloride for six hours at 140–150°. The reaction mixture was poured into several volumes of water and the product recrystallized from ethanol.

SUMMARY

Six classes of ethers of highly halogenated phenols were prepared and tested for fungistatic activity.

Twelve of the compounds prepared are new.

On the basis of the test employed, the phenoxyethanols reported in this work show definite promise as fungistatic or fungicidal compounds.

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[Contribution from the Department of Chemistry of the University of Buffalo]

THE ACTION OF ETHYL ORTHOFORMATE ON ANILINE AND CERTAIN OF ITS DERIVATIVES

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INTRODUCTION

The purpose of this investigation was first to determine the nature and course of the reaction between ethyl orthoformate and aniline. Because the former contains three functional groups and the latter two labile hydrogens, it might be expected that different products would result from the use of these two compounds against each other in different molar ratios. An attempt has been made to clarify this problem. Secondly, it was desired to obtain similar information with regard to the action of ethyl orthoformate on certain substituted anilines, namely the three isomeric nitroanilines and the three chloroanilines.

A summary of the literature covering the subject of this paper has already been presented (1) and for this reason only a short survey will be given here. Suffice it to say here however that reactions of this type have been found to yield both amidines (2, 3, 4, 5, 7) and derivatives of triphenylmethane (6). To make matters worse, physical properties are often very confusing. Thus 139° is listed by Giacolone (6) as the melting point of triphenyltriaminomethane and 138° by others for diphenylamidine (3).

The situation is therefore one of confusion, as pointed out by Dr. Edwin R. Erickson, in a private communication to the last author, some time ago. Most investigators seem to feel that an amidine is produced on the interaction of ethyl orthoformate and aniline in the molar ratio of 1:2, but Giacolone (6) believed the reaction to proceed with three moles of aniline to form an entirely different compound. Data on the nitro substitution products are very confusing, as will be seen from a review of the information presented above. Some analytical figures favor one formula, some the other.

Similar situations exist with respect to the products formed from the isomeric toluidines (3, 6, 7) and from the monobromoanilines (3, 7, 8, 9, 10).

ETHYL ORTHOFORMATE AND ANILINE

It was at first desired to repeat the work of R. Walther (7) and of Giacolone (6). Thus, heating aniline and ethyl orthoformate on the steam-bath (Walther) for 2.5 hours and recrystallizing the product twice from benzene, gave a compound with the melting point 139.0° (cor.). When heated at reflux temperatures in 3:1 molar ratio (Giacolone) there was produced a white crystalline product. This product, recrystallized in the same manner, showed the melting point 139.0° (cor.). A second run was made using an air condenser for reflux instead of water. The results of determinations of mixed melting points are shown in Table I.

TABLE I

MELTING POINTS

REACTING COMPOUND	MELTING POINT, °C.
$C_6H_5NH_2$ (b)	139.0
$C_6H_5NH_2$ (c)	139.0
$C_6H_5NH_2$ (d)	138.8
$C_6H_5NH_2$ (b + c)	138.7
$C_6H_5NH_2$ (c + d)	139.0
$C_6H_5NH_2$ (2c + b)	138.5
$C_6H_5NH_2$ (c + 3d)	138.8
o-$ClC_6H_4NH_2$ (a)	141.1
o-$ClC_6H_4NH_2$ (b)	141.1
o-$ClC_6H_4NH_2$ (a + b)	140.9
o-$ClC_6H_4NH_2$ (a + 2b)	141.2
o-$ClC_6H_4NH_2$ (2a + b)	141.1
m-$ClC_6H_4NH_2$ (a)	111.4
m-$ClC_6H_4NH_2$ (b)	111.4
m-$ClC_6N_4NH_2$ (a + b)	111.1
m-$ClC_6H_4NH_2$ (a + 2b)	111.5
m-$ClC_6H_4NH_2$ (2a + b)	111.4
p-$ClC_6H_4NH_2$ (a)	183.9
p-$ClC_6H_4NH_2$ (b)	183.9
p-$ClC_6H_4NH_2$ (a + b)	184.0
p-$ClC_6H_4NH_2$ (a + 2b)	183.9
p-$ClC_6H_4NH_2$ (2a + b)	183.7

a = reflux temperatures, molar ratio 1.76:1.
b = water-bath temperature, molar ratio 1.76:1.
c = reflux temperatures, molar ratio 3.20:1.
d = water-bath temperature, molar ratio 3.20:1.

TABLE II

MOLECULAR WEIGHTS

REACTING COMPOUND	FOUND	LITERATURE	K_f BENZENE
$C_6H_5NH_2$ (b)	293 ± 6	196	4.90
$C_6H_5NH_2$ (b)	312 ± 6	196	5.23
$C_6H_5NH_2$ (a)	267 ± 3	289	4.90
o-$ClC_6H_4NH_2$ (b)	392 ± 4	265	4.90
o-$ClC_6H_4NH_2$ (a)		393	
m-$ClC_6H_4NH_2$ (b)	393 ± 4	393	4.90
p-$ClC_6H_4NH_2$ (b)	393 ± 4	393	4.90

a = product prepared at reflux temperatures.
b = product prepared on the water-bath.

As a preliminary to the determination of molecular weights, the exact solubility of the reaction product, prepared by the method of Walther, in benzene was found to be 3.7 g. per 100 g. of solvent at 7° (cor.).

Determination of the molecular weights of products formed at reflux temperatures was not considered necessary in view of the results of the determinations of mixed melting points.

These data make the average freezing point lowering 0.294° ± 0.006, the correction being estimated on the basis of 0.001° for each reading. Temperatures were read with the aid of a lens. The following formula was used:

$$\text{Mol. Wt.} = \frac{(1000)\ (K_f)\ (W)}{(dT_f)\ (W_0)}$$

In this equation, K_f is the cryoscopic constant of the solvent (two were used, *i.e.* 4.9° and 5.23° per mole of benzene), W the weight in grams of solute in W_0 grams of solvent and dT_f the freezing point lowering in degrees C. Thus

$$\text{Mol. Wt.} = \frac{(1000)\ (K_f)\ (0.4225)}{(0.294)\ (24.06)}$$

If K_f be taken as 4.9, the Mol. Wt is calculated as 293 ± 6, and if the constant be taken as 5.23, 312 ± 6. Theory for Giacolone's compound is 289 and for Walther's 196.

TABLE III

FREEZING POINTS

BENZENE	SOLUTION, WALTHER'S PRODUCT
4.900	4.607
4.901	4.606
4.898	4.606
4.900 (av)	4.606 (av)

Determination of the nitrogen content was not attempted. Triphenyltriaminomethane has a nitrogen content of 14.52% and diphenylamidine 14.27%. It was decided not to rely on any method where the choices were so close together. Titration as a base failed. The product is not even wetted by cold water and dissolves in hydrochloric acid very slowly.

Giacolone (6) was able to cause triphenyltriaminomethane to rearrange in aniline solution, with hydrochloric acid or aniline hydrochloride as a catalyst. The identical reaction was easily carried out. Color changes observed check with Giacolone's observations and are recorded in the Experimental Part. They may be due to oxidation of the rearranged product to $(p\text{-}H_2NC_6H_4)_2C{=}C_6H_4{=}NH_2Cl$. The product of the rearrangement is p,p′,p″-triaminotriphenylmethane. Triphenyltriaminomethane hydrochloride was prepared, by passing dry hydrogen chloride into a dilute benzene solution of the product from the steam-bath reaction, with precipitation of a white solid, m.p. 244° (cor.). This product had been washed but not recrystallized. Giacolone recorded the melting point 240° for assumedly the same product. Aniline hydrochloride, for use in rearrangement reaction, was prepared in the same manner using an ether solution of aniline. The salt melted at 197.8° (cor.), literature 198°.

ETHYL ORTHOFORMATE AND THE ISOMERIC NITROANILINES

The isomeric nitroanilines proved poor reactants with ethyl orthoformate. The products were never obtained in a pure state and apparently the reactions were never complete. Melting points varied by entire degrees from one run to the next and determinations of molecular weights could never be made to check.

ETHYL ORTHOFORMATE AND THE ISOMERIC CHLOROANILINES

Again, as in the aniline reaction, it was found that the product prepared by the interaction of ethyl orthoformate and a chloroaniline was the same whether prepared at reflux temperatures or on the water-bath. A determination of molecular weights indicated that the formulas advanced by Giacolone could be considered correct, namely $CH(NHC_6H_4Cl)_3$.

A summary of data relative to mixed melting points will be found on reference to Table I and with regard to molecular weights, to Table II.

p,p′,p″-Trichlorotriphenyltriaminomethane underwent rearrangement as did the corresponding compound without chlorine, but satisfactory identification of the product was not attempted because of the difficulty in purification. Probably the reaction did not go to completion.

EXPERIMENTAL PART

Thermometers used solely for melting point determinations, were standardized by the National Bureau of Standards. Numerical corrections to observed values were applied as directed.

Ethyl orthoformate was purchased from the Eastman Kodak Co , suitably purified and checked with respect to its physical properties, with the same compound prepared in our laboratories.

Aniline, Merck, was subjected to purification, b p. 180°.

Nitroanilines were taken from stock and recrystallized from ethyl alcohol. Satisfactory, corrected melting points were obtained.

o-Chloroaniline and *m*-chloroaniline were purified by distillation, *p*-chloroaniline by recrystallization from ethyl alcohol. Physical properties were satisfactory.

Reactions with aniline. Walther's procedure was repeated using a molar aniline : ester ratio of 1.76:1 and Giacolone's with a ratio of 3.20:1. Aniline : ester ratios were used corresponding to both Walther's and Giacolone's procedures, each ratio being tried out (a) at reflux temperatures and (b) on the water-bath. After extensive purification, molecular weights were determined by the cryoscopic method in benzene according to Reilly and Rae (11) and Findlay (12). The hydrochlorides were prepared by passing dry hydrogen chloride into a benzene solution of the reaction product. Rearrangements were brought about by following the method of Giacolone (6).

Reactions with nitroanilines. *p*-Nitroaniline and ethyl orthoformate were refluxed in molar ratio of 1.76:1, using twenty grams of each, over an open flame for 2.3 hours. Even after this length of time, both solid and liquid phases were still present and there seemed to be no evidence that a reaction had taken place. A second run was also carried out under like circumstances but no definite melting points were obtained. Products were brown in color and obviously impure, in spite of attempts at purification, carried out along the lines which had proved successful in the case of the product resulting from the use of aniline.

Reactions with chloroanilines. *o*-Chloroaniline, 3 grams, was refluxed with 3 grams of ethyl orthoformate for 1.3 hours over an open flame. A fine white crystalline precipitate settled out of the red-brown solution on cooling to room temperature. This was washed with cold ethyl orthoformate and recrystallized twice from benzene, m.p. 141.1° (corrected). The filtrate was fractionated and enough ethyl alcohol was distilled off at 78° to verify the assumption of a 65% yield of product, based on the *o*-chloroaniline used, probably—

I. $HC(OC_2H_5)_3 + 3\ o\text{-}ClC_6H_4NH_2 \rightarrow 3C_2H_5OH + HC(NHC_6H_4Cl\text{-}o)_3$.

A second run was carried out as above except that the reaction was heated on the steam-bath for four hours. Also, this time, the reaction mixture was cooled more slowly with the result that the crystals were larger and better formed. The yield amounted to about 70%, based on the *ortho*-chloroaniline used. Mixed melting point with the product from the first reaction gave 141.0° and a molecular weight determination of this second product showed 392 (see Table II). *m*-Chloroaniline and *p*-chloroaniline were treated in the same manner. Data from all of these runs will be found summarized in Tables I and II.

SUMMARY

1. It has been shown, within the limits of experimental error, that aniline reacts with ethyl orthoformate to form $CH(NHC_6H_5)_3$, irrespective of the molar proportions in contact. Changing the temperature of reaction from reflux to water-bath also has no effect on the chemical nature of the product.

2. Attempts to extend this reaction to isomeric nitroanilines were unsatisfactory.

3. The isomeric chloroanilines react as does aniline itself.

4. Rearrangement of compounds thus prepared can be effected by the catalytic action of aniline hydrochloride.

BUFFALO, NEW YORK

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

HYDROLYSIS AND CHLORINATION OF THREE β-CHLOROETHYLAMINES[1]

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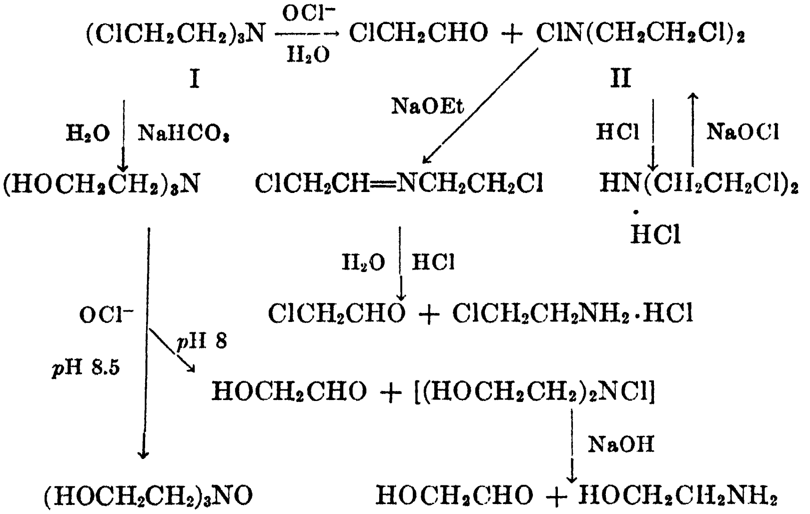
An investigation of the behavior of *tris*(β-chloroethyl)amine (I) and ethyl- (III) and methyl- (VII) *bis*(β-chloroethyl)amines has established the nature of a number of hydrolysis products. It has further been found that chlorine in water attacks these substances rapidly, leading to cleavage of one of the alkyl groups and formation of a secondary chloramine. This reaction is illustrated by the conversion of I into *bis*(β-chloroethyl)chloramine (II). Other transformations of I and its hydrolysis product, triethanolamine, are summarized below.


$(ClCH_2CH_2)_3N$
OCl^-
H_2O
$ClCH_2CHO$ + $ClN(CH_2CH_2Cl)_2$
I
II
NaOEt
H_2O
$NaHCO_3$
HCl
NaOCl
$(HOCH_2CH_2)_3N$
$ClCH_2CH{=}NCH_2CH_2Cl$
$HN(CH_2CH_2Cl)_2 \cdot HCl$
H_2O
HCl
OCl^-
pH 8.5
pH 8
$ClCH_2CHO$ + $ClCH_2CH_2NH_2 \cdot HCl$
$HOCH_2CHO$ + $[(HOCH_2CH_2)_2NCl]$
NaOH
$(HOCH_2CH_2)_3NO$
$HOCH_2CHO$ + $HOCH_2CH_2NH_2$

The *bis*(β-chloroethyl)amine was identified as the *p*-nitrobenzoate, β-chloroethylamine as the picrate, chloroacetaldehyde as the 2,4-dinitrophenylhydrazone, glycol aldehyde as the *p*-nitrophenylosazone and by characteristic color reactions, and the ethanolamine as its picrate. *bis*(β-Chloroethyl)chloramine was isolated by vacuum distillation as a colorless liquid which gradually turned black and deposited white crystals identified as *bis*(β-chloroethyl)amine hydrochloride.

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[1] The work reported in this paper was done under a contract recommended by the National Defense Research Committee, between the Office of Scientific Research and Development and the University of Illinois.

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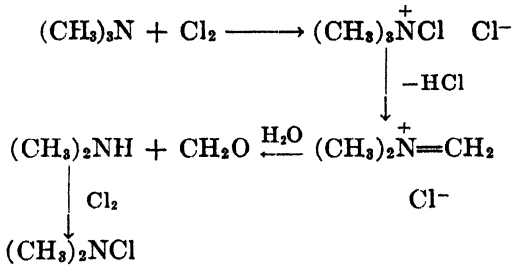
[4] Present address, The Upjohn Co., Kalamazoo, Michigan.

The course for the chlorinolysis is probably similar to that suggested by Meisenheimer (1) for the analogous cleavage of trimethylamine.

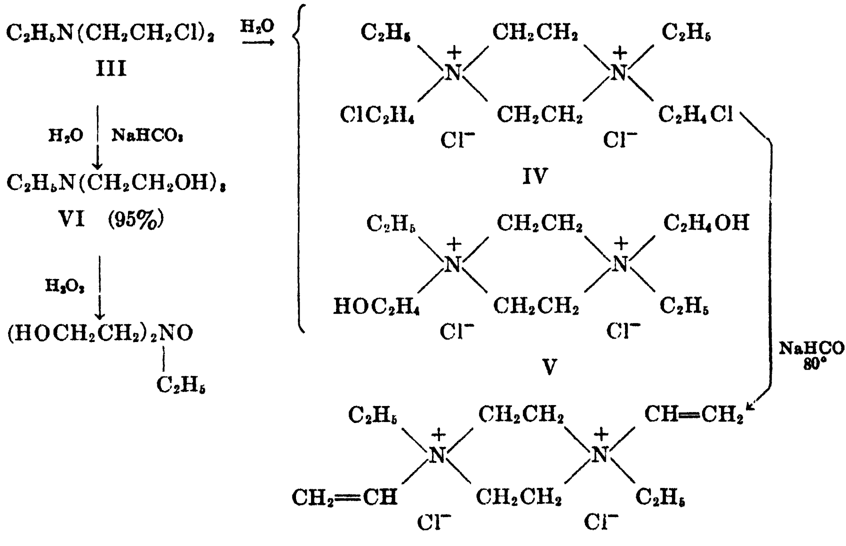


$$\begin{tikzcd}[column sep=small] (CH_3)_3N + Cl_2 \arrow[r] & (CH_3)_3\overset{+}{N}Cl\ \ Cl^- \arrow[d, "-HCl"] \\ (CH_3)_2NH + CH_2O \arrow[d, "Cl_2"] & (CH_3)_2\overset{+}{N}{=}CH_2\ \ Cl^- \arrow[l, "H_2O"'] \\ (CH_3)_2NCl & \end{tikzcd}$$

Hydrolysis of the chlorine atom in the quaternary chlorammonium salt would account for the amine oxide formed from triethanolamine at higher *p*H.

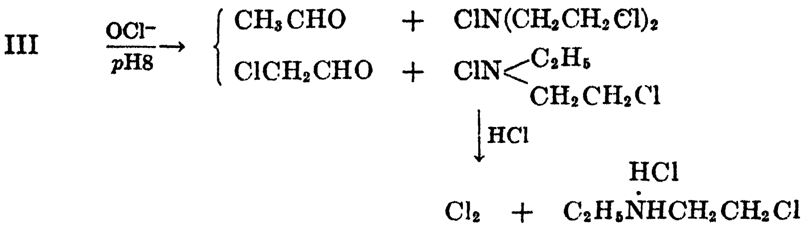
Berg (2) has reported cleavage of a number of secondary chloramines analogous to that outlined above.

The hydrolysis of III in bicarbonate-buffered solution proceeded almost exclusively to the corresponding glycol, ethyldiethanolamine. In unbuffered solution, however, the hydrolysis took a more complex course and two dimeric quaternary ammonium salts (IV and V) were isolated and identified.



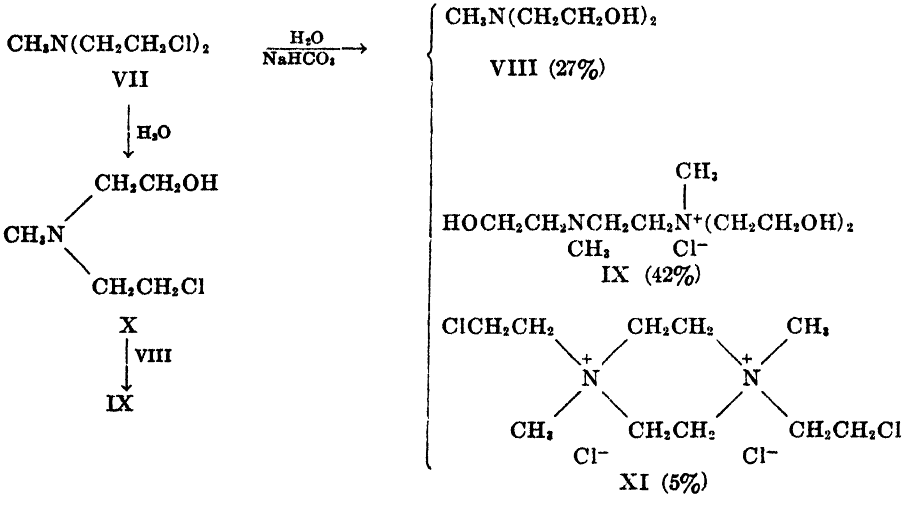
Hot aqueous bicarbonate dehydrohalogenated the cylic dimer IV to the divinyl analog. Acetaldehyde and acetylene were identified as gaseous by-products. The former may have arisen from hydrolysis of a vinylamine group. The latter undoubtedly resulted from a cleavage of the piperazinium ring similar to that reported by Mason (3).

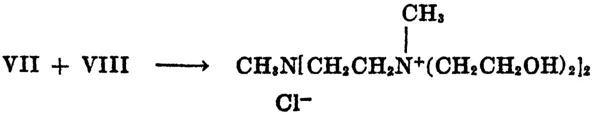
Chlorination of III proceeded readily, leading to cleavage of either a chloroethyl or the ethyl group.



The hydrolysis of VII differed from that of III in that dimeric salts (IX and XI) in addition to the glycol (VIII) were isolated from hydrolysis even in bicarbonate-buffered solution.

In unbuffered solution, the chlorohydrin (X, as the hydrochloride) was one of the principal products. The cyclic dimer XI was prepared from VII in alcohol in two possible stereoisomeric forms[5] although only one was isolated from the hydrolysis mixture. A third quaternary salt, XII, was prepared by reaction of VII with methyldiethanolamine (VIII) in aqueous solution.





$$\text{VII} + \text{VIII} \longrightarrow \underset{\text{Cl}^-}{\text{CH}_3\text{N}}[\text{CH}_2\text{CH}_2\overset{\text{CH}_3}{\text{N}^+}(\text{CH}_2\text{CH}_2\text{OH})_2]_2$$

XII

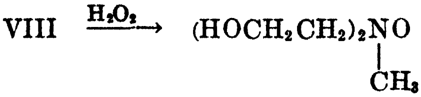
---

[5] The melting points observed for the dipicrates were not as high as those reported by Hanby and Rydon (4).

Chlorination of VII apparently resulted principally in cleavage of the methyl group.

$$\mathrm{VII} \xrightarrow{\mathrm{OCl^-}} \mathrm{CH_2O} + \mathrm{ClN(CH_2CH_2Cl)_2}$$

The amine oxide from VIII, prepared by action of hydrogen peroxide, was characterized as the picrate.



$$\mathrm{VIII} \xrightarrow{\mathrm{H_2O_2}} \mathrm{(HOCH_2CH_2)_2\overset{}{N}O} \atop \qquad\qquad\qquad\qquad \mathrm{|\;CH_3}$$

EXPERIMENTAL

Hydrolysis of tris(β-chloroethyl)amine (I) in bicarbonate solution. A solution of 4.8 g. (0.02 mole) of *tris*(β-chloroethyl)amine hydrochloride in water was added to a solution of 6.72 g. (0.08 mole) of sodium bicarbonate and diluted to two liters. The free base did not dissolve completely on mixing but slowly went into solution during a period of six days. The solution was acidified with hydrochloric acid to *p*H 2 and concentrated to dryness at 25° under diminished pressure. The residue was extracted with hot ethanol, which deposited crystals of triethanolamine hydrochloride on cooling. The yield of triethanolamine hydrochloride, m.p. and mixed m.p. 174.0–176.5°, was 2.17 g. (59%). The residue weighed 5.95 g. or 1.27 g. in excess of the theoretical amount of sodium chloride. The residue was dissolved in water and treated with picric acid but no picrate was isolated.

Chlorination of (I). (a) *In acid solution.* A solution of 10 g. of I hydrochloride in 400 cc. of water was treated with gaseous chlorine. The chlorine was bubbled slowly through the solution for 30 minutes. The solution became cloudy after five minutes and an oil settled to the bottom. After standing three hours at room temperature, the aqueous solution was decanted from the oil and extracted with 100 cc. of ether. The ether extract was added to the oil and washed with 20 cc. of water. Evaporation of the ether yielded 4.0 g. of *bis*(β-chloroethyl)chloramine. The addition of 20 cc. of hot 6 *N* hydrochloric acid caused evolution of chlorine and formation of *bis*(β-chloroethyl)amine hydrochloride. The latter was identified by preparation of the *p*-nitrobenzoate, m.p. 187–189°. The derivative changed from the low-melting (m.p. 92–95°) to the high-melting form after the first recrystallization (5).

The aqueous portion of the reaction products was concentrated to dryness under diminished pressure. The first 150 cc. of distillate was treated with 2 g. of 2,4-dinitrophenylhydrazine. The precipitate was recrystallized to yield 0.2 g. of glyoxal 2, 4-dinitrophenylosazone, m.p. 305–311° dec., [lit. (6), 318°] and 1.3 g. of β-chloroacetaldehyde 2, 4-dinitrophenylhydrazone, m.p. 151–155° [lit. (5), 155°]. The crystalline residue was shown to contain unchanged I by conversion to the picrate.

(b) *In neutral solution.* Two hundred cc of sodium hypochlorite solution (0.095 mole of chlorine) was adjusted to *p*H 8.5 with 6 *N* hydrochloric acid and buffered with 6.72 g. (0.08 mole) of sodium bicarbonate. The solution was stirred and 4.8 g. (0.02 mole) of I hydrochloride was added in small portions during five minutes. The temperature rose from 18° to 25° during the addition. *bis*(β-Chloroethyl)chloramine separated as an oil after the first few minutes. The hypochlorite content of the solution was determined at intervals for twenty-five minutes by titration of the iodine liberated from potassium iodide with sodium thiosulfate. The hypochlorite was consumed rapidly. The small value for positive chlorine at the end of this time was probably due to the solubility of the chloramine.

The reaction mixture was extracted with two 100-cc. portions of ether and the ether extracts dried with magnesium sulfate. The ether solution of *bis*(β-chloroethyl)chloramine was unstable and 0.05 g. of *bis*(β-chloroethyl)amine hydrochloride separated in shiny flat needles, m.p. 206–212° (dec.). After one recrystallization from methanol-ether solution, the melting point was 210–212° (dec.) [lit. (7, 8), 216°].

The ether was evaporated under diminished pressure, the final traces of solvent being removed at one mm. A pale yellow oil weighing 3.70 g. remained. Five cc. of concentrated hydrochloric acid was added and the mixture warmed until a clear solution was obtained. The solution was diluted with water and concentrated to dryness under diminished pressure. The *bis*(β-chloroethyl)amine hydrochloride was recrystallized twice from methanol-ether solution, flat needles, m.p. 210–212° (dec.). The *p*-nitrobenzoate derivative was prepared by allowing 1 g. of the amine hydrochloride, 1.3 g. of *p*-nitrobenzoyl chloride, and 4.0 g. of sodium bicarbonate in 50 cc. of wet ether to stand at room temperature for one hour. The ether was evaporated under diminished pressure and the residue extracted with hot methanol, which deposited *bis*(β-chloroethyl)amine *p*-nitrobenzoate on cooling. The compound was recrystallized three times from methanol solution as long white needles, m.p. 96–97° [lit. (5, 9), 98°].

In a similar experiment, 12.05 g. (0 05 mole) of I was treated with sodium hypochlorite solution following the same procedure. The chloramine was distilled from a Claisen flask under diminished pressure. The yield of *bis*(β-chloroethyl)chloramine, b.p. 60–63° (1.3 mm.), was 3.45 g. (39%). There was considerable decomposition during the distillation, a dark residue of 3.6 g. remaining. A weighed sample of the distilled chloramine was dissolved in water and the positive chlorine was determined by titration of the iodine liberated from potassium iodide with sodium thiosulfate. The purity of the sample of *bis*(β-chloroethyl)chloramine was calculated from this titration to be 87.0%.

Preparation of bis(β*-chloroethyl*)*chloramine*. *bis*(β-Chloroethyl)amine hydrochloride was prepared by the method of Mann (7). A solution of 17.9 g. (0.10 mole) in 10 cc. of water was added with stirring to 245 cc. of 0.90 *N* sodium hypochlorite solution (0.11 mole of chlorine) buffered with 8.4 g (0.10 mole) of sodium bicarbonate. After five minutes the reaction mixture was extracted with two 100-cc. portions of ether and the ether extracts dried with magnesium sulfate. The ether was distilled at ordinary pressure and the residual pale yellow oil distilled from a Claisen flask under diminished pressure. The *bis*(β-chloroethyl)chloramine boiled at 64–69° (2.3 mm.). The yield was 11.4 g. (64.3%).

A weighed sample was dissolved in water and the positive chlorine was determined by titration of the iodine liberated from potassium iodide with thiosulfate. The purity of the sample was calculated from this titration to be 99.0%.

An excess of *bis*(β-chloroethyl)chloramine in water was stirred and the aqueous layer analyzed for positive chlorine after five and ten minutes. The value was the same for both determinations. The solubility, as estimated from these titrations, was 2.12 g. per liter.

Decomposition of bis(β*-chloroethyl*)*chloramine in aqueous bicarbonate*. A sample of 6.8 g. (0.0385 mole) of *bis*(β-chloroethyl)chloramine and 8.4 g. (0.10 mole) of sodium bicarbonate in 100 cc. of water was refluxed for four hours. At the end of this period, the undissolved chloramine had disappeared and the resulting solution was dark brown. The solution was concentrated to dryness under diminished pressure at 50° and the residue extracted with 100 cc. of absolute ethanol. The ethanol was evaporated under diminished pressure leaving, 4.6 g. of dark brown oil The oil could not be distilled under diminished pressure.

Reaction of bis(β*-chloroethyl*)*chloramine and sodium ethoxide*. A sample of *bis*(β-chloroethyl)chloramine was treated with an equimolecular amount of sodium ethoxide in ethanol. The reaction mixture became warm and sodium chloride separated. The solution darkened on standing and during the evaporation of the ethanol under diminished pressure. The residual dark brown oil could not be distilled under diminished pressure. A nonvolatile tar resulted from the attempted distillation.

In a similar experiment, the isolation of the expected Schiff base was not attempted. The reaction mixture was subjected to hydrolysis and β-chloroethylamine and β-chloroacetaldehyde were identified as the products. To a solution of 4.5 g. (0.025 mole) of *bis*(β-chloroethyl)amine hydrochloride in 40 cc. of water was added 42 cc. of 1.35 *N* calcium hypochlorite solution (0.025 mole of chlorine). The chloramine was extracted with two 40-cc. portions of ether. An alcoholic solution containing 0.025 mole of sodium ethoxide was prepared by treating 0.575 g. (0.025 mole) of sodium with 25 cc. of absolute ethanol. The alcoholic sodium ethoxide solution was slowly added to the ether solution of the chloramine, which was cooled in an ice-bath. After standing one hour at room temperature, the starch-iodide test for positive chlorine was negative. The reaction mixture was acidified with 100 cc. of 1 N hydrochloric acid. The ether was evaporated under diminished pressure and then 50 cc. of the remaining solution distilled at ordinary pressure. The distillate was treated with 2,4-dinitrophenylhydrazine and the resulting chloracetaldehyde 2,4-dinitrophenylhydrazone recrystallized twice from ethanol in fine yellow needles, m.p. 153.5–155.5° [lit. (5), 155°].

The aqueous residue from the distillation was treated with Norit and evaporated to dryness under diminished pressure. The residue was extracted with ethanol. The addition of ether to the ethanol solution precipitated an oil which slowly crystallized on standing. After one recrystallization from alcohol-ether solution, there was obtained 1.1 g. of white shiny plates which melted at 134–138°. This compound was further purified, and melted at 142–144° [lit. (8), 144°]. The picrate was prepared by adding 0 5 N calcium picrate to an aqueous solution of the amine hydrochloride. The picrate was recrystallized twice from water solution in long yellow needles. The picrate was dried in a vacuum for three hours at 78°. The β-chloroethylammonium picrate melted at 144.0–145.5° [lit. (8), 143°]

Attempted reaction of I with chloramine-T. A solution of 14.9 g. (0.06 mole) of chloramine-T and 6.72 g. (0 08 mole) of sodium bicarbonate in 300 cc. of water was cooled in an ice-bath to 10°. The solution was stirred and 4.8 g. (0.02 mole) of I hydrochloride was added. The ice-bath was removed and the reaction mixture was allowed to warm to room temperature. An aliquot sample was analyzed at intervals for positive chlorine by titration of the liberated iodine with sodium thiosulfate. The positive chlorine value did not decrease during one hour. The I was extracted with two 100-cc. portions of ether and dried with magnesium sulfate. The ether solution was saturated with hydrogen chloride. The crystalline precipitate of I hydrochloride was dried with phosphoric anhydride in a vacuum, weight of impure hydrochloride obtained, 4.05 g. After two recrystallizations from alcohol-ether solution there was obtained 0.4 g. of I hydrochloride, m p. and mixed m.p 129–31°.

Preparation of triethanolamine oxide. The method was essentially that used by Lauer (10). Thirty cc. of 30% hydrogen peroxide was added slowly with cooling to 28.8 g. (0.193 mole) of triethanolamine and the resulting solution allowed to stand overnight. The clear sirupy oil was washed with a 50-cc. and then two 100-cc. portions of acetone and then crystallized from hot acetone-ethanol solution. The white crystalline product was dried over calcium chloride *in vacuo*. The yield of triethanolamine oxide, m p. 103–105°, was 20.7 g. (65%).

Reaction of triethanolamine with basic sodium hypochlorite solution. A solution of 14.9 g. (0.10 mole) of triethanolamine in 150 cc. of water was added to 218 cc. of 0.91 N sodium hypochlorite solution (0.10 mole of chlorine). The sodium hypochlorite solution, pH 11.5, was buffered with 8.4 g. (0.10 mole) of sodium bicarbonate so that the pH of the resulting solution was 8.5. After thirty minutes the solution was concentrated to dryness under reduced pressure at 50°. The almost white, semi-solid residue was extracted with 100 cc. of absolute ethanol. The extract was concentrated under reduced pressure to a viscous oil. Attempts to crystallize this oil from acetone-ethanol were unsuccessful. The oil was finally crystallized from butanol. The crystalline product was filtered, washed with acetone and dried over calcium chloride *in vacuo*. The yield of triethanolamine oxide, m.p. 100–103°, was 7.4 g. (45.0%). A sample recrystallized from butanol melted at 104–105° and was not depressed when mixed with an authentic sample of triethanolamine oxide.

Reaction of triethanolamine with neutralized hypochlorite solutions. The procedure used in the reaction of triethanolamine with basic hypochlorite solutions was repeated. The only change was that the sodium hypochlorite was adjusted to pH 8 with 6 N hydrochloric acid and then buffered with sodium bicarbonate. The product was a dark oil which was soluble in acetone and could not be made to yield the amine oxide.

In another experiment a solution of 7.5 g. (0.05 mole) of triethanolamine and 8.4 g. (0.10 mole) of sodium bicarbonate in 70 cc. of water was cooled in an ice-bath during the addition of 230 cc. of 1.04 N sodium hypochlorite solution (0.12 mole of chlorine) which had been adjusted to pH 8 with 6 N hydrochloric acid. The addition was complete in 15 minutes. The solution was analyzed for positive chlorine and found to contain 0.015 mole of unreacted chlorine. A solution of p-nitrophenylhydrazine hydrochloride at this point yielded a yellow precipitate which changed to red on standing.

A 50-cc. portion was acidified with hydrochloric acid and the solution distilled. Twenty-five cc. of distillate was collected. The distillate slowly reduced Fehling's solution in the cold. The p-nitrophenylosazone was prepared and recrystallized from pyridine solution in dark red needles, m.p. 304–305° (dec.). The derivative was mixed with an authentic sample of glyoxal p-nitrophenylosazone, m.p. 305–306° (dec.) [lit., 308° (11), 311° (12)].

The remainder of the original solution was made basic with 15 g. of sodium hydroxide. The resulting solution became a deep yellow color, characteristic of glycollic aldehyde. The solution was distilled almost to dryness. The distillate gave a positive test for monoethanolamine with sodium nitroprusside (13) and was basic to litmus. The distillate was acidified with hydrochloric acid and concentrated to dryness under diminished pressure. The solid residue, weight 0.9 g., was dissolved in ethanol and neutralized with a solution of sodium hydroxide. The picrate was prepared. Sodium picrate precipitated from the ethanol solution first. The filtrate was then concentrated and cooled to yield ethanolamine picrate. This picrate was twice recrystallized from ethanol, m.p. and mixed m.p. 157.5–159° [lit. (14), 159.5°].

Reaction of diethanolamine with hypochlorite. A solution of 5.26 g. (0.05 mole) of diethanolamine and 4.2 g. (0.05 mole) of sodium bicarbonate in 50 cc. of water was cooled in an ice-bath during the addition of 106 cc. of 1.02 N sodium hypochlorite solution (0.054 mole of chlorine) which had been adjusted to pH 8 with 6 N hydrochloric acid. The addition was complete in ten minutes. At this time the solution was analyzed for positive chlorine and found to contain 0.053 mole of chlorine. A solution of 2.0 g. (0.05 mole) of sodium hydroxide was added during ten minutes and analysis of the solution then showed it to contain 0.006 mole of chlorine.

A 75-cc. portion was acidified with hydrochloric acid and concentrated to dryness at room temperature under diminished pressure. The pale yellow semi-solid residue was extracted with 50 cc. of ethanol. The ethanol was evaporated to yield an oil. This oil could not be crystallized and gradually discolored on standing.

A 25-cc. portion was acidified with hydrochloric acid and distilled almost to dryness. The distillate reduced Tollens' reagent and Fehling's solution in the cold. The p-nitrophenylosazone was prepared and recrystallized from pyridine solution in dark red needles, m.p. 304–306° dec. The melting point was not depressed when mixed with an authentic sample of glyoxal p-nitrophenylosazone.

The remainder of the original solution was made basic with 5 g. of sodium hydroxide. The resulting solution became deep yellow. The solution was distilled almost to dryness. The distillate gave a positive test for monoethanolamine with sodium nitroprusside (13) and was basic to litmus. The distillate was acidified with hydrochloric acid and concentrated to dryness under diminished pressure. The solid residue, weight 1.3 g., was identified as ethanolamine hydrochloride by preparation of the picrate. The ethanolamine picrate was recrystallized from ethanol as heavy needles, m.p. and mixed m.p. 158–159°.

Hydrolysis of III in unbuffered solution. A solution of 32.5 g. (0.19 mole) of III in 4 l. of distilled water was allowed to stand at room temperature for twelve days. The solution was neutralized to phenolphthalein with potassium carbonate and then concentrated to 150 cc. under diminished pressure. Extraction with chloroform failed to remove any free base. After evaporating to dryness, absolute ethanol was added and the precipitate collected on a filter. The filtrate was concentrated and ethanol added. This was repeated three times.

The first and second precipitates, weighing 10.56 g., proved to be potassium chloride and contained no dimer as indicated by negative tests for nitrogen in the sodium fusion method. The remaining precipitates yielded 1.55 g. of impure III dichloro cyclic dimer (IV), *dipicrate*, m.p. 225–226° (dec.).

The filtrate, when concentrated to dryness, contained a syrupy oil, very soluble in water and alcohol, which could not be crystallized.

Addition of acetone to a small portion of this oil dissolved in absolute ethanol precipitated a hygroscopic solid, m.p. 79–81° (dec.). Addition of a saturated picric acid solution to a water solution of this solid gave a picrate, m.p. 183–184°. It was purified by washing with hot alcohol and water and analyzed correctly for III dihydroxy cyclic dimer (V) dipicrate.

Anal. Calc'd for $C_{24}H_{32}N_8O_{16}$: C, 41.86; H, 4.68; N, 16.28.
Found: C, 41.68; H, 4.70; N, 16.37.

The remaining oil was dissolved in ethanol and acetone was added. However, the solid which separated immediately turned oily. Acetone was added until no more oil separated. The alcohol-acetone mixture was separated. The oil which remained formed a picrate, m.p. 183–184°.

Hydrolysis of III in aqueous sodium bicarbonate solution. A solution containing 16.04 g. (0.094 mole) of III and 15.89 g. (0.189 mole) of sodium bicarbonate in 2 l. of distilled water was allowed to stand at room temperature for 13 days. At this time the *p*H was 6.1. After aerating the solution with a stream of air to remove the dissolved carbon dioxide, the *p*H was 7.4. The solution was acidified to *p*H 2 with hydrochloric acid, and concentrated under diminished pressure at 30° to a volume of 25 cc. Absolute ethanol was added and the precipitate collected; the filtrate was concentrated and absolute ethanol added. This procedure was repeated three times. The combined precipitate weighed 11.06 g. The precipitate gave no test for nitrogen by the sodium fusion method, indicating that no dimer had been formed. Concentration of the final filtrate yielded ethyldiethanolamine hydrochloride (hygroscopic) which was dried over calcium chloride for one week. An alcoholic solution of sodium ethoxide, prepared by treating 2.2 g. (0.096 mole) of sodium with 50 cc. of absolute ethanol, was added to the amine hydrochloride. The sodium chloride which separated was immediately filtered and the filtrate distilled under diminished pressure to yield 11.0 g. of ethyldiethanolamine which boiled at 113–118° (7 mm.). The residue in the flask was dissolved in absolute ethanol. The ethanol was evaporated leaving a residue of 0.8 g. of ethyldiethanolamine, identified by preparation of the picrate, m.p. and mixed m.p. 100–101°. The yield of ethyl diethanolamine was 11.8 g. (94.4%).

Preparation of III dichloro cyclic dimer [1,4-bis(β-chloroethyl)-1,4-diethylpiperazinium dichloride, IV]. An alcoholic solution of III was allowed to stand at room temperature for six weeks. At this time, a 70% yield of dimer had separated, m.p. 300–308° (dec.). The molecular weight in aqueous solution was determined by the Beckmann freezing point depression method. Extrapolation to zero concentration gave a value of 109.8 for the molecular weight. The calculated value for the dimer is 113.3.

The dimer was purified by precipitation from aqueous solution by the addition of acetone. After drying over phosphoric anhydride at 100°, it melted at 308–312° (dec.) [Hanby and Rydon (4) report 312°].

Anal. Calc'd for $C_{12}H_{26}Cl_4N_2$: C, 42.37; H, 7.70; N, 8.24; Cl, 41.70.
Found: C, 42.02; H, 7.91; N, 8.01; Cl, 42.61.

A solution of 0.2 g. of the dimer in 5 cc. of water was added to 22 cc. of a saturated solution of picric acid. The *picrate* was collected on a filter and dried over calcium choride *in vacuo* for fifteen hours. There was obtained 0.29 g. (67%) of picrate which softened at 221° and melted at 224–225° with decomposition. The picrate was recrystallized from water, m.p. 225–226° (dec.) [Hanby and Rydon (4) report 232°].

Anal. Calc'd for $C_{24}H_{30}Cl_2N_8O_{14}$: C, 39.73; H, 4.17; N, 15.46; Cl, 9.78.
Found: C, 39.76; H, 4.02; N, 15.24; Cl, 9.76.

Hydrolysis of IV in aqueous sodium bicarbonate. At room temperature, no hydrolysis of IV was found to take place in thirteen days. This was shown to be the case by titration of the chloride ion using the method of Mohr. The dimer was recovered unchanged as the picrate, m.p. 224–225° (dec.), in almost quantitative yield.

At 50° the hydrolysis proceeded to an appreciable extent. After eight days it was found that 38.4% hydrolysis had occurred as calculated from the increase in chloride ion concentration.

A solution of 10.65 g. (0.031 mole) of IV and 10.42 g (0.124 mole) of sodium bicarbonate in 200 cc. of distilled water was heated to 80° in a flask fitted with a water-cooled condenser, and the evolved gases were passed through a solution of 2,4-dinitrophenylhydrazine. The solution was heated for six hours. A precipitate of acetaldehyde 2,4-dinitrophenylhydrazone had formed and was identified by m.p. and mixed m.p , 167–168° (corr.). In another experiment the evolved gases were passed through ammoniacal cuprous chloride. A colloidal red precipitate of copper acetylide indicated the presence of acetylene.

The cherry-red aqueous solution from the hydrolysis was extracted for four days with ether in a continous extractor. The ether extract was dried with sodium sulfate and distilled. The red oil which remained was refluxed with 6 *N* hydrochloric acid. The evolved gases gave a precipitate when passed through 2,4-dinitrophenylhydrazine solution. The oil was evidently a polymer of acetaldehyde.

The aqueous solution from the ether extraction was divided into two portions. One portion was treated with picric acid to yield a picrate, m.p. 202–205°, (dec.). This compound has the proper analysis for divinyldiethylpiperazinium dipicrate.

Anal. Calc'd for $C_{24}H_{28}N_8O_{14}$: C, 44.17; H, 4.30; N, 17.18.

Found: C, 44.42, 44.28; H, 4.46, 4.53; N, 17.17.

No other products from this reaction have been identified.

Chlorination of III in neutral solution. A solution containing 0.27 mole of chlorine (465 cc. of 1.16 *N* sodium hypochlorite) was adjusted to *p*H 8 with 6 *N* hydrochloric acid and buffered with 15.1 g. (0.18 mole) of sodium bicarbonate. The solution was rapidly stirred during the addition of 9.3 g. (0.045 mole) of III hydrochloride. After one and one-half hours the solution was extracted with two 100-cc. portions of ether and the ether extracts dried with magnesium sulfate. The ether was carefully distilled and the last traces removed by heating the water-bath to 70°. A distillation was carried out at room temperature using an oil-pump, collecting the distillate in a Dry Ice-chloroform trap. The distillate was identified as ethyl-β-chloroethylchloramine by treatment with concentrated hydrochloric acid to form ethyl-β-chloroethylamine and chlorine. The solution containing the amine hydrochloride was evaporated to dryness under diminished pressure. The residue was dissolved in ethanol and the amine hydrochloride precipitated by the addition of ether. The ethyl-β-chloroethylamine hydrochloride was recrystallized from ethanol-ether solution, m.p. 215–216° (dec.). There was no depression of m.p. in mixture with authentic ethyl-β-chloroethylamine hydrochloride which melted at 217–219° (dec.). The yield of ethyl-β-chloroethylchloramine collected in the low temperature distillation was 5.90 g. (0.042 mole).

The oil remaining from the room temperature distillation was distilled from a Claisen flask. A pale yellow fraction weighing 1.05 g., which boiled at 60–63° (1.75 mm.), was obtained. This was identified as *bis*(β-chloroethyl)chloramine by conversion to *bis*(β-chloroethyl)amine hydrochloride, using the same procedure as with ethyl-β-chloroethylchloramine. The *bis*(β-chloroethyl)amine hydrochloride was recrystallized from ethanol-ether solution, m.p. and mixed m.p. 211–213° (dec.). A weighed sample of *bis*(β-chloroethyl)-chloramine was dissolved in water and the positive chlorine was determined by titration of the iodine liberated from potassium iodide with thiosulfate. The purity of the sample of chloramine was calculated from this titration to be 83.7%. The yield of *bis*(β-chloroethyl)amine was 1.05 g. (13.3%).

The aqueous solution remaining after the ether extraction of the chloroamines was acidified with hydrochloric acid and treated with a solution of 3.0 g. of *p*-nitrophenylhydrazine in 50 cc. of 0.5 N hydrochloric acid. The precipitate, weighing 4.0 g., was fractionally crystallized to yield fine orange needles of acetaldehyde *p*-nitrophenylhydrazone, m.p. and mixed m.p. 125.0–126.5°, and deep red needles of glyoxal *p*-nitrophenylosazone, m.p. 304–306° (dec.), in roughly equal amounts (*ca.* 1.7 g. of glyoxal and 2.2 g. of acetaldehyde derivative).

In a similar experiment the ethyl-β-chloroethylchloramine was distilled at a higher pressure. The chlorination of 14.5 g. (0.07 mole) of III with 0.32 mole of chlorine (860 cc. of 0.73 N sodium hypochlorite) yielded 1.65 g. (0.0116 mole) of ethyl-β-chloroethylchloramine which boiled at 64.1–66.3° (26 mm.). A weighed sample of the chloramine was dissolved in water and the positive chlorine was determined. The purity of the sample of ethyl-β-chloroethylchloramine was calculated from this titration to be 94.3%. The yield was 16.6%

The residual pale yellow oil from this distillation weighed 7.30 g. It was probably mainly *bis*(β-chloroethyl)chloramine. Calculated as such, the yield of crude chloramine was 7.30 g. (59%).

Preparation of ethyl-β-chloroethylchloramine. Ethyl-β-chloroethylamine hydrochloride was prepared according to the method of Lasselle and Sundet (15).

A cold solution of 0.11 mole of chlorine (262 cc. of 0.84 N sodium hypochlorite solution) was adjusted to *p*H 8.5 with 6 N hydrochloric acid and buffered with 10.1 g. (0.12 mole) of sodium bicarbonate. The solution was rapidly stirred during the addition of 14.4 g. (0.10 mole) of ethyl-β-chloroethylamine hydrochloride. After fifteen minutes the reaction mixture was extracted with two 100-cc. portions of ether and the ether extracts dried overnight with magnesium sulfate.

The ether was distilled at ordinary pressure and the residual pale yellow oil distilled under diminished pressure. The ethyl-β-chloroethylchloramine boiled at 64.5–66.5° (26 mm.). The yield was 9.95 g. (70%). It decomposed slowly on standing, crystals of ethyl-β-chloroethylamine hydrochloride forming in the liquid.

A weighed sample of the chloramine was dissolved in water and the positive chlorine was determined. The purity of the sample was calculated from this titration to be 98.0%.

An excess of ethyl-β-chloroethylchloramine in water was stirred and the aqueous layer analyzed for positive chlorine after five and ten minutes. The value remained the same for both determinations. The solubility was calculated from these titrations to be 5.58 grams per liter.

Reaction of ethyl-β-chloroethylchloramine with sodium hypochlorite. To 8.65 g. (0.061 mole) of ethyl-β-chloroethylchloramine and 200 cc. of water was added 407 cc. of 0.87 N sodium hypochlorite solution (0.183 mole of chlorine) buffered with 16.8 g. (0.20 mole) of sodium bicarbonate. After stirring the reaction mixture for two hours, a determination of positive chlorine showed that approximately 0.07 mole of chlorine had been consumed. An insoluble oil remained.

The reaction mixture was extracted with two 100-cc. portions of ether and the ether extracts dried with magnesium sulfate. The ether was distilled at atmospheric pressure and the residue, 3.30 g. of pale yellow liquid, distilled under diminished pressure. There was obtained 1.85 g. (21.4%) of ethyl-β-chloroethylchloramine which boiled at 54.0–57.5° (24 mm.). The chloramine was converted to the amine hydrochloride with hydrochloric acid. The hydrochloride melted at 217–219° dec., and was not depressed when mixed with an authentic sample.

The aqueous layer was acidified with hydrochloric acid and aerated to remove the chlorine. *p*-Nitrophenylhydrazine hydrochloride gave a precipitate, which was recrystallized to yield acetaldehyde *p*-nitrophenylhydrazone, m.p. and mixed m.p. 123–125°, and glyoxal *p*-nitrophenylosazone, m.p. and mixed m.p. 304–306° (dec.).

Reaction of ethyl-bis(β-hydroxyethyl)amine and hydrogen peroxide. To 13.3 g. (0.10 mole) of ethyldiethanolamine cooled in an ice-bath, was added 12 cc. of 30% hydrogen peroxide (0.10 mole). The solution was allowed to stand at room temperature overnight. The product was extracted with 50 cc. of ether and two 50-cc. portions of acetone. The resulting clear sirupy product was dissolved in butanol and some of the solvent distilled to remove any water. The amine oxide could not be crystallized from butanol. A large volume of ether was added to the butanol solution and the butanol and ether layer decanted from the amine oxide. It was dried in vacuum over calcium chloride, and did not crystallize on standing a month.

A picrate was prepared using 1.5 g. of the oil, 2.5 g. of picric acid and 25 cc. of ethanol. The ethanol was evaporated and the solid residue recrystallized from ethyl acetate-chloroform solution to yield 2.70 g. (71%) of ethyldiethanolamine oxide picrate which melted at 79–88°. A sample twice recrystallized melted at 90–91°.

Anal. Calc'd for $C_{12}H_{18}N_4O_{10}$: C, 38.10; H, 4.80; N, 14.81.
Found: C, 38.32; H, 4.79; N, 14.18, 14.10.

Hydrolysis of VII in bicarbonate solution. A solution of 19.3 g. (0.10 mole) of VII hydrochloride and 25.3 g. (0.30 mole) of sodium bicarbonate in two liters of water was allowed to stand at room temperature six days. The solution was acidified with hydrochloric acid to *p*H 2 and then concentrated to dryness under diminished pressure. A solution of 6.8 g. (0.10 mole) of sodium ethoxide in 100 cc. of ethanol was added to the solid residue, and after ten minutes it was saturated with carbon dioxide. The reaction mixture was filtered. The ethanol was evaporated from the filtrate under diminished pressure, and the residue, a light brown oil weighing 10.7 g., was extracted with ether. The ether extraction yielded 3.90 g. of an oil, which was distilled and yielded 3.20 g. (27%) of methyldiethanolamine which boiled at 115–118° (5 mm.). The residue, weight 0.40 g. was ether-soluble, indicating that it was probably also methyldiethanolamine. Another similar experiment yielded 21% of methyldiethanolamine.

The residue after the ether extraction readily dissolved in a small amount of ethanol and was filtered from the sodium chloride which had precipitated. The oil was insoluble in ether and acetone. Numerous attempts at crystallization were unsuccessful. The The evaporation of the solvents yielded 5.4 g. of oil. It was finally identified as the open-chain trihydroxy dimer by preparation of the dipicrylsulfonate. The picrylsulfonate was recrystallized from ethanol-water solution and dried over phosphoric anhydride *in vacuo.*

Anal. Calc'd for $C_{22}H_{30}N_8O_{21}S_2$: C, 32.76; H, 3.75; N, 13.87.
Found: C, 32.83, 32.84; H, 3.80, 3.75; N, 13.32.

The melting point was not depressed when mixed with the picrylsulfonate of the linear trihydroxy dimer, m.p. 203–204° (dec.), which had been prepared by reaction of the chlorohydrin X with methyldiethanolamine (18). The yield of linear trihydroxy dimer from the hydrolysis mixture was 5.4 g. (42%).

The solid from the treatment of the residue with alcoholic sodium ethoxide was neutralized with dilute hydrochloric acid and evaporated to dryness. The residue weighed 26.0 g. or 2.6 g. in excess of the theoretical amount of sodium chloride. The residue in 200 cc. of water was heated to boiling and 6.0 g. of picric acid was added. The precipitate was fractionally crystallized to yield 1.45 g. (4.2%) of the dichloro cyclic dimer (XI) dipicrate, m.p. and mixed m.p. 212–213° (dec.). From another experiment the yield was 5%.

Hydrolysis of VII in unbuffered solution. A solution of 28.9 g. (0.15 mole) of VII hydrochloride and 6.0 g. (0.15 mole) of sodium hydroxide in 2 l. of water was allowed to stand for 42 hours at 25°. The solution was concentrated to 60 cc. under diminished pressure at 25°. The solid was collected on a filter and dried over calcium chloride *in vacuo,* weight 7.6 g. (32.4%). This was identified as the dichloro cyclic dimer (XI). The compound exhibited no definite melting point. When heated from room temperature it was badly charred by 300°. If it was inserted at 320°, it had melted with decomposition by 323°. It was purified by precipitating it from water solution with a large volume of acetone.

Anal. Calc'd for $C_{10}H_{22}Cl_4N_2$: C, 38.48; H, 7.11, N, 8.97; Cl, 45.44.
Found: C, 38.65; H, 7.19; N, 8.23, 8.24; Cl, 44.11.

The *picrate* was prepared and recrystallized from water in golden-yellow needles or plates, m.p. 212–213° (dec.).

Anal. Calc'd for $C_{22}H_{26}Cl_2N_8O_{14}$: C, 37.89; H, 3.76; N, 16.07; Cl, 10.17.
Found: C, 38.16; H, 3.84; N, 15.18; Cl, 10.21.

The filtrate was adjusted to pH 7 with sodium hydroxide and extracted with chloroform to remove VII. The solution was adjusted to pH 10.5 and extracted with chloroform. The chloroform was distilled leaving only a trace of dark brown solid.

In another experiment, a solution of 28.9 g. (0.15 mole) of VII hydrochloride and 6.0 g. (0.15 mole) of sodium hydroxide in 2 l. of water was allowed to stand for 42 hours at 25°. The solution was concentrated to 50 cc. under diminished pressure. The dichloro cyclic dimer (XI) was dried over calcium chloride *in vacuo*. The yield of dimer was 5.8 g. (25%). The *picrate* was prepared and recrystallized from ethanol-water solution in flat needles, m.p. 211–212° (dec.).

The filtrate was adjusted to pH 7 with 5 *N* sodium hydroxide and extracted with three 50-cc. portions of chloroform. The aqueous layer was cooled and acidified with 50 cc. of concentrated hydrochloric acid. The sodium chloride was separated and the solution was evaporated to dryness under diminished pressure. The semi-solid residue was extracted with 50 cc. of hot ethanol. The residue, 1.5 g., yielded a picrate of the isomeric dimer, m.p. 194–196° (dec.). The isomeric dimer prepared from alcoholic solutions of VII yielded a picrate, m.p. 195–197° dec.

The ethanol filtrate was concentrated to dryness under diminished pressure. The residue, 9.0 g. of hygroscopic sirupy liquid, failed to crystallize on standing over phosphoric anhydride *in vacuo*. The picrate was prepared by dissolving the oil in 150 cc. of ethanol and adding 13.2 g. of picric acid to the boiling solution. The first fraction of orange crystals, weight 8.7 g., melted at 68–71°. The filtrate was concentrated and a second fraction, weight 5.5 g., which melted at 64–67°, was collected. Three recrystallizations from ethyl acetate-benzene solution yielded 5.3 g. of VII chlorohydrin picrate, m.p. 68–70°. The yield of crude chlorohydrin (X) picrate was 14.2 g. (26%).

Preparation of X picrate. The procedure was essentially that described in a British report (16). A solution of 21.0 g. (0.134 mole) of VII in two liters of water was allowed to stand at room temperature for 42 hours. Then 280 cc. of 0.5 *N* calcium picrate solution was added, and the initial precipitate of dimer dipicrate and VII picrate collected. The yield of picrate was 13.0 g , m.p. 170–185°. The filtrate was concentrated under diminished pressure to 500 cc. The first fraction of 12.2 g. of chlorohydrin (X) picrate melted at 66–70°. The filtrate was concentrated to 250 cc. and a second fraction weighing 11.4 g. was obtained, m.p. 67–70°. The picrate was recrystallized from ethyl acetate-benzene solution in orange prisms to yield 18.4 g. (37.5%) of chlorohydrin picrate. The melting points of various fractions of crystals from the recrystallizations ranged from 69–72° to 73–75°.

The reaction of VII with methyldiethanolamine. Fifteen grams (0.096 mole) of VII was added to a solution of 34.27 g. (0.288 mole) of methyldiethanolamine in 200 cc. of water. The reaction mixture was stirred at room temperature for six hours and the clear solution was allowed to stand overnight, and was concentrated under diminished pressure at 50–60°. The syrup was dissolved in 50 cc. of absolute ethanol and concentrated under diminished pressure. This was repeated. The syrup was covered with 100 cc. of acetone, and slowly crystallized on scratching and cooling. After one recrystallization from absolute ethanol, the yield of the bis-ammonium compound (XII) m.p 92–94°, was 33 g. (87%). The compound was further purified by recrystallization from absolute ethanol in the form of rosettes, which melted at 94–96°. [Bergmann (17) reported m.p. 93–95°].

Anal. Calc'd for $C_{15}H_{37}Cl_2N_3O_4$ C, 45.67; H, 9.46; N, 10.66; Cl, 17.98.
Found: C, 45.75; H, 9.11; N, 9.95; Cl, 18.03.

An excess of saturated picric acid in absolute ethanol was added to a solution of the ammonium compound dissolved in absolute ethanol. An oil separated and slowly crystallized on standing. The *tripicrate* was recrystallized from water-ethanol solution, m.p. 140–143° (dec.).

Anal. Calc'd for $C_{33}N_{44}N_{12}O_{25}$: C, 39.29; H, 4.40; N, 16.66.
Found: C, 39.29; H, 4.56; N, 16.53.

Preparation of VII dichloro cyclic dimer (XI). A solution of sodium ethoxide from 1.2 g. (0.05 mole) of sodium in 20 cc. of absolute ethanol was added to 9.7 g. (0.05 mole) of VII hydrochloride. The sodium chloride was removed and washed with 10 cc. of absolute ethanol. The filtrate became cloudy almost immediately and a solid separated. After two days, 5.6 g. (72%) of dimer had separated. It was purified by precipitation from aqueous solution by addition of acetone, weight 3.6 g. The dimer exhibited an indefinite melting point as noted before. A sample inserted into the bath at 312° melted with decomposition up to 316°. The *picrate* was prepared and recrystallized from ethanol-water in plates, m.p. 211.5–212.5° (dec.).

The preparation of the dimer was repeated using the free base in alcohol instead of neutralized hydrochloride solutions. An aqueous solution of 7.0 g. (0.03 mole) of VII hydrochloride was neutralized with the calculated amount of sodium hydroxide solution, VII was extracted with chloroform, and the chloroform dried with magnesium sulfate and evaporated under diminished pressure. The VII was dissolved in 20 cc. of ethanol. After 30 hours, 2.8 g. of dimer had formed. It was purified by precipitation from aqueous solution by addition of acetone. The picrate was prepared and was recrystallized from ethanol-water in golden yellow plates or needles, m.p. 195.5–197.5° (dec.). The melting point of the picrate did not change when crystallization was induced by seeding with the high-melting picrate.

Anal. Calc'd for $C_{22}H_{26}Cl_2N_8O_{14}$: C, 37.89; H, 3.76; N, 16.07.
Found: C, 38.10; H, 3.80; N, 16.38.

Reaction of VII and hydrogen peroxide. To a solution of 8.5 g. (0.0545 mole) of VII in 50 cc. of methanol was added excess 30% hydrogen peroxide. The solution was cooled in an ice-bath and allowed to stand overnight. The white precipitate which formed, weight 3.35 g., was identified as the β-dichloro cyclic dimer by preparation of the picrate, m.p. and mixed m.p. 212–213.5° (dec.). The filtrate was concentrated and treated with acetone to yield 4.30 g. of β-dichloro cyclic dimer, identified by preparation of the picrate, m.p. and mixed m.p. 196–198° (dec.). The yield of dimer was 7.65 g. (90%).

The reaction was repeated with acetone as the solvent to yield 88% of dichloro cyclic dimer.

Hydrolysis of VII dichloro cyclic dimer. (XI). A solution of 10.5 g. of dimer and 11.0 g. of sodium bicarbonate in 200 cc. of water was heated to 90° for 24 hours. The solution became deep red. The evolved gases yielded a precipitate with 2,4-dinitrophenylhydrazine hydrochloride solution, which was recrystallized from ethanol and identified as acetaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 163–164°. Other products of this reaction were not identified.

Chlorination of VII. Two hundred and fifty cc. of 0.95 *N* sodium hypochlorite solution (0.119 mole of chlorine) was adjusted to *p*H 8.0 with 6 *N* hydrochloric acid and buffered with 8.4 g. (0.10 mole) of sodium bicarbonate. The solution was stirred during the addition of 5.78 g. (0.03 mole) of VII hydrochloride. The temperature rose from 19° to 40° during this addition.

The reaction mixture was extracted with two 100-cc. portions of ether and the ether extracts dried with magnesium sulfate. The ether was evaporated under diminished pressure to yield 3.6 g. of pale yellow oil, which evolved chlorine when treated with 5 cc. of concentrated hydrochloric acid. The product was diluted with water and evaporated to dryness under diminished pressure. The solid residue weighed 2.5 g. One gram of this residue was treated with 20 cc. of 0.5 *N* calcium picrate solution. The picrate, weight 2.5 g., melted at 94–98°. It was fractionally crystallized, and yielded only the picrate of *bis*(β-chloroethyl)amine, m.p. 107–109.° The *p*-nitrobenzoate was prepared, m.p. 96–97°.

The aqueous solution was distilled under diminished pressure and the distillate was treated with 2,4-dinitrophenylhydrazine. The solid obtained was fractionally crystallized, to yield formaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 162–164°, and glyoxal 2,4-dinitrophenylosazone, m.p. 319–320° (dec.).

Preparation of methyldiethanolamine oxide. Excess 30% hydrogen peroxide was added slowly with cooling and stirring to methyldiethanolamine. The solution was evaporated under diminished pressure at 60°. The sirupy residue was extracted twice with acetone. The attempts at crystallization of this sirup were unsuccessful.

The picrate was prepared and recrystallized from absolute ethanol, m.p. 74–75°.

Anal. Calc'd for $C_{11}H_{16}N_4O_{10}$: C, 36.27; H, 4.43.

Found: C, 36.25; H, 4.52.

SUMMARY

A number of hydrolysis products of *tris*(β-chloroethyl)amine and ethyl- and methyl-*bis*(β-chloroethyl)amines have been isolated and characterized.

Treatment of these amines with aqueous hypochlorite rapidly cleaves the tertiary amines to an aldehyde and a secondary chloramine.

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[Contribution from the Lederle Laboratories Division, American Cyanamid Co.]

BIOTIN. VII. SYNTHESIS OF *dl-epi*BIOTIN

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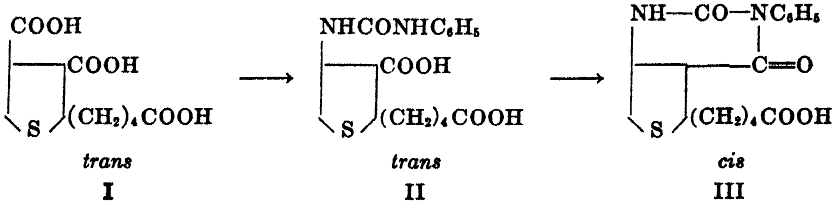
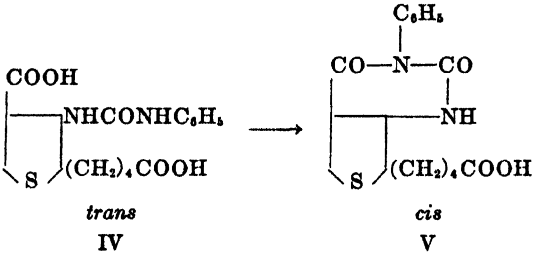
In a previous communication (1) were described the syntheses of *dl*-biotin and *dl-epi*allobiotin. The key intermediate for their preparation was 3-phenyl-6-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (III) prepared by inversion of the configuration of the 3-carboxyl group of 2-(δ-carboxybutyl)-4-uranilinothiophane-*trans*-3-carboxylic acid (II) to *cis* followed by ring closure.





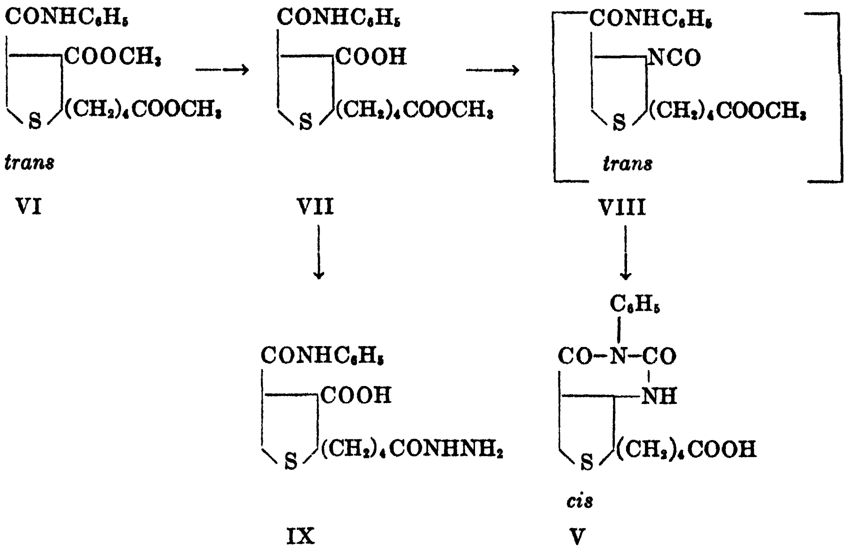
It should theoretically be possible to obtain the configuration of *dl-epi*biotin, which is epimeric to *dl*-biotin at the C_2 position, by inversion of the 4-carboxyl of a molecule such as 2-(δ-carboxybutyl)-3-uranilinothiophane-*trans*-4-carboxylic acid (IV) (synthesized from the triacid, I, by Curtius degradation of the 3-carboxyl group) to *cis* followed by ring closure to the thienouracil, V, no matter what the absolute configuration of the C_2 side chain is in I, II and IV. This is readily demonstrated as in Chart I.

CHART I

C_2 + −		C_2 + −		C_2 + −
C_3 − +	$\xleftarrow[C_4]{\text{invert}}$	C_3 − +	$\xrightarrow[C_3]{\text{invert}}$	C_3 + −
C_4 − +		C_4 + −		C_4 + −
Va		Ia		IIIa
C_2 − +		C_2 − +		C_2 − +
C_3 − +	$\xleftarrow[C_4]{\text{invert}}$	C_3 − +	$\xrightarrow[C_3]{\text{invert}}$	C_3 + −
C_4 − +		C_4 + −		C_4 + −
Vb		Ib		IIIb

The *trans*-triacid racemate, I, may have either the total configuration Ia or Ib. The uranilinodiacids, II and IV, have the same configuration as I. If the configuration of the triacid is Ia, then inversion at C_3 (in the transformation II → III) will give configuration IIIa. In contrast Ia, when inverted at C_4 (in the transformation IV → V) will give configuration Va. Both Va and IIIa

CHART II



are related *cis* at C_3 and C_4, but are epimeric at C_2. The same argument may be applied if the configuration of the *trans*-triacid is Ib. Thus, both *cis* isomers of the biotin structure may be synthesized by utilization of this principle, which was modified for simplification in syntheses of *dl-epi*biotin as shown in Chart II.

2-(δ-Carbomethoxybutyl)-3-carbomethoxy-*trans*-4-carbanilidothiophane (VI) (1), when treated with one equivalent of alkali, was predominately selectively hydrolyzed at the 3-carbomethoxy group to give VII. The monoester was characterized as the hydrazide, IX, soluble in both acid and alkali. The free carboxyl group was converted to the azide *via* the acid chloride with sodium azide. When the azide was heated in acetic anhydride containing sodium acetate, it rearranged to the intermediate isocyanate, VIII. The reagents then caused inversion of the 4-carbanilido group from *trans* to *cis* followed by ring closure to a *cis*-uracil.[1] The 1-acetyl and ester side chain groups were removed by acid hydrolysis. The resultant product was 3-phenyl-8-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (V). When the hydrazide, IX, was converted to the azide and the latter treated under the same conditions, no crystalline product could be isolated. The ring closure of the isocyanate, VIII, to the uracil, V, proves that the monoester, VII, has the structure indicated and not that of the isomeric 2-(δ-carboxybutyl)-3-carbomethoxy-*trans*-4-carbanilidothiophane.

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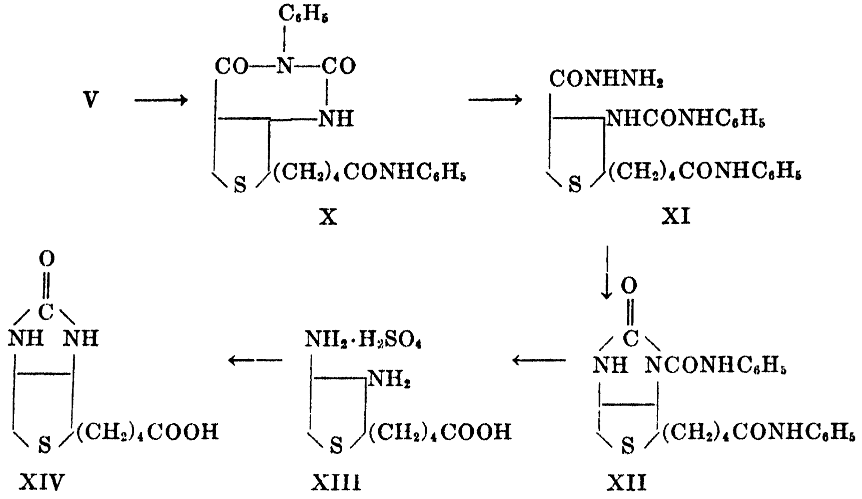
[1] The feasibility of this reaction was demonstrated on a model compound without the side chain, namely 4-carbanilidothiophane-3-isocyanate.

The uracil, V, was converted to *dl-epi*biotin (XIV) in the same manner that the uracil, III, of epimeric configuration was transformed into *dl*-biotin (1). The carboxyl group was blocked as the anilide, X. The uracil ring was easily ruptured with hydrazine forming the *cis*-hydrazide, XI.[2] The latter was degraded to 2-(δ-carbanilidobutyl)-4-carbanilido-5-ketoimidazolido[4,5,c,*cis*]thiophane (XII) by butyl nitrite and hydrogen chloride in butanol. The blocking groups were removed by hydrolysis with barium hydroxide solution at 170° and the resultant diamine sulfate, XIII, treated with phosgene. The final product was *dl-epi*biotin, XIV, m.p. 190–191°.



*dl-epi*Biotin was biologically inactive when assayed with *S. cerevisiea.* That it was epimeric to *dl*-biotin at the C_2 position was demonstrated by desulfurization with Raney nickel to the biologically active *dl*-desthiobiotin (2).

Dittmer, Melville, and duVigneaud (3) have shown that yeast can utilize desthiobiotin by converting it to biotin. The fact that *epi*biotin is inactive indicates that this microorganism cannot transform *epi*biotin to biotin *via* desthiobiotin by removal and reintroduction of the sulfur atom to give the biotin configuration.

Thus, starting with *only a single configuration,* that of 2-(δ-carboxybutyl)-thiophane-3,4-*trans*-dicarboxylic acid (I), *any one of three configurations* related to biotin can be prepared at will, namely, *dl*-biotin, *dl-epi*allobiotin, and *dl-epi*biotin. No attempt has been made to prepare the last of the four possible configurations, that of the known allobiotin (4), starting with I.

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[2] It is interesting to note that the aniline residue used for a blocking group on the C_4 functional group has now been transformed into the blocking group for the C_3 functional group.

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EXPERIMENTAL

2-(δ-Carbomethoxybutyl)-4-carbanilidothiophane-trans-3-carboxylic acid (VII). To a warm solution of 7 g. of 2-(δ-carbomethoxybutyl)-3-carbomethoxy-*trans*-4-carbanilidothiophane (VI) (1) in 70 cc. of methanol was added 7 cc. of 10% sodium hydroxide solution. After seventeen hours at room temperature, the solution was concentrated on the steam-bath with an air stream to remove most of the methanol, then diluted with water containing sodium bicarbonate. The unchanged starting material (1.7 g.) was removed and the filtrate acidified; yield, 4.7 g. (69%) of product, m.p. 180–195°, suitable for the next step. For analysis a sample was leached with hot ethyl acetate and the insoluble portion recrystallized from hot Methyl Cellosolve by dilution with water, white crystals, m.p. 207–209°.

Anal. Calc'd for $C_{18}H_{23}NO_5S$: C, 59.2; H, 6.3; N, 3.8.
Found. C, 59.1; H, 6.1; N, 3.5.

The 1.7 g. of unchanged diester was retreated as described above. An additional 1.1 g. (16%) of product, m.p. 185–205° was obtained.

2-(δ-Carboxhydrazidobutyl)-4-carbanilidothiophane-trans-3-carboxylic acid (IX). A solution of 280 mg. of pure 2-(δ-carbomethoxybutyl)-4-carbanilidothiophane-*trans*-3-carboxylic acid (VII) in 0 6 cc. of 100% hydrazine hydrate was heated on the steam-bath for twenty minutes, then diluted with about 20 cc. of water, acidified with 2 cc. of acetic acid, and cooled in an ice-bath. The product consisted of white crystals, m.p. 243–245°dec.; yield, 230 mg. (82%). This compound readily dissolves in dilute acid or alkali.

Anal. Calc'd for $C_{17}H_{23}N_3O_4S$: C, 55.8; H, 6.3.
Found: C, 55 4; H, 6.0.

trans-3-Carbomethoxy-4-carbanilidothiophane A mixture of 8 g. of *trans*-3-carbomethoxythiophane-4-carboxylic acid (5), 8 cc. of thionyl chloride and 40 cc. of benzene was refluxed for twenty minutes, then evaporated to dryness *in vacuo.* The evaporation was repeated after the addition of 50 cc. of benzene. The residual acid chloride, dissolved in 50 cc. of benzene, was treated with 16 cc. of aniline. After two minutes, the mixture was diluted with 50 cc. of ethyl acetate and washed with dilute hydrochloric acid. The turbid organic layer was evaporated to dryness *in vacuo* and the residue extracted with 150 cc. of hot benzene. The filtered solution was diluted with 300 cc. of petroleum ether and the product collected; yield, 7.2 g. (65%), m.p. 147–149°. Recrystallization from benzene gave voluminous white needles, m.p. 150–151°.

Anal. Calc'd for $C_{13}H_{15}NO_3S$. N, 5.3. Found: N, 5.5.

Hydrolysis with hot dilute alcoholic alkali gave *trans*-4-carbanilidothiophane-3-carboxylic acid in 93% yield, m p. 223–224°.

Anal. Calc'd for $C_{12}H_{13}NO_3S$· C, 57.3; H, 5 2.
Found: C, 57.4; H, 4.9.

trans-4-Carbanilidothiophane-3-carboxhydrazide. A mixture of 3.8 g. of *trans*-3-carbomethoxy-4-carbanilidothiophane and 16 cc. of 100% hydrazine hydrate was heated to boiling. The resultant solution was heated on the steam-bath for forty-five minutes, then diluted to about 75 cc. with water. The solid was washed with water; yield, 3.7 g. (97%), m.p. 198–200°. For analysis a sample was recrystallized from 50% alcohol, white crystals, m.p. 200–201°.

Anal. Calc'd for $C_{12}H_{15}N_3O_2S$: N, 15 8. Found: N, 15 7.

1-Acetyl-3-phenyl-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil. To a solution of 320 mg. of *trans*-4-carbanilidothiophane-3-carboxhydrazide in 4 cc. of 0.5 *N* hydrochloric acid cooled in an ice-bath was added with stirring over a period of five minutes a solution of 100 mg. of sodium nitrite in 1 cc. of water. The gummy azide was extracted with reagent ethyl acetate and the extracts dried with magnesium sulfate at 0°. The solution was refluxed for twenty minutes, then evaporated to dryness *in vacuo*. The residual isocyanate was refluxed with 150 mg. of anhydrous sodium acetate and 3 cc. of acetic anhydride for twenty minutes. Dilution with about 20 cc. of water gave white crystals, m.p. 236–239°; yield, 230 mg. (66%). A mixture with this same compound prepared by a different method (5) gave no depression in m.p.

trans-3-Carbethoxyamino-4-carbanilidothiophane. *trans*-4-Carbanilidothiophane-3-carboxhydrazide (3.2 g.) was converted to the azide in ethyl acetate solution as described above. The solution was diluted with 35 cc. of absolute ethanol, refluxed fifty minutes, then evaporated. The solid residue was heated to boiling with 50 cc. of absolute ethanol, then cooled in an ice-bath; yield, 1.5 g. (42%), m.p. 221–223°. Additional material was obtained from the filtrate. For analysis a sample was recrystallized from aqueous Methyl Cellosolve, white crystals, m.p. 225–226°.

Anal. Calc'd for $C_{14}H_{18}N_2O_3S$: C, 57.2; H, 6.2; N, 9.5.
Found: C, 57.9; H, 6.4; N, 9.5.

Attempts to convert this urethan to 1-acetyl-3-phenyl-5,6,8,9-tetrahydrothieno[3,4,e,-cis]uracil by boiling with acetic anhydride containing sodium acetate for two hours *via* inversion of the configuration and elimination of the elements of ethanol resulted in unchanged starting material.

3-Phenyl-8-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,cis]uracil (*V*). A mixture of 7.0 g. of 2-(δ-carbomethoxybutyl)-4-carbanilidothiophane-*trans*-3-carboxylic acid (VII), 25 cc. of dry ether containing 0.5% pyridine, and 18 cc. of thionyl chloride was shaken occasionally for thirty minutes. The mixture was evaporated to dryness *in vacuo* (bath 50°) and the evaporation repeated after addition of 25 cc. of chloroform. The residual acid chloride, dissolved in 50 cc. of acetone at 0°, was added to a stirred and ice-cooled solution of 5 g. of sodium azide in 50 cc. of water over a period of five minutes, 10 cc. more of acetone being used as a rinse. After being stirred for thirty minutes at 0°, the mixture was diluted to 250 cc. with ice-water containing 15 cc. of saturated sodium bicarbonate solution. The slightly gummy azide was washed with ice-water and dried at room temperature at 1 mm. To the dry azide was added 105 cc. of acetic anhydride and 3.5 g. of anhydrous sodium acetate. On being heated, the mixture rapidly evolved nitrogen. After being refluxed for one hour, the hot mixture was cautiously diluted with 52 cc. of water. When the acetic anhydride had decomposed, the solution was diluted with 52 cc. of concentrated hydrochloric acid and refluxed thirty minutes more. The solution was concentrated *in vacuo* until the product started to separate, then it was diluted to about 250 cc. with ice-water. The product was washed with water and slurried with ethyl acetate, then washed with ethyl acetate (about 100 cc.) until no more color was removed; yield, 2.7 g. (41%), m.p. 203–208°. Recrystallization from aqueous methanol did not change the m.p.

Anal. Calc'd for $C_{17}H_{20}N_2O_4S$· C, 58 7; II, 5.8; N, 8.0.
Found: C, 59.0; H, 5.4; N, 8.3, 7.9.

2-(δ-Carbanilidobutyl)-3-uranilinothiophane-cis-4-carboxhydrazide (*XI*). A mixture of 0.90 g. of 3-phenyl-8-(δ-carboxybutyl)-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (V), 18 cc. of chloroform, 9 cc. of thionyl chloride, and 0.05 cc. of pyridine was refluxed for five minutes, then the solution was evaporated to dryness *in vacuo*. Suspended in 20 cc. of acetone, the acid chloride was treated with 3 cc. of aniline and heated on the steam-bath for about five minutes until all the acid chloride had reacted. The mixture was poured into 160 cc. of water containing 10 cc. of concentrated hydrochloric acid. The 3-phenyl-8-(δ-carbanilidobutyl)-5,6,8,9-tetrahydrothieno[3,4,e,*cis*]uracil (X) was washed with water; yield, 1.05 g. (90%). The anilide could not be satisfactorily purified for analysis.

A mixture of 1 05 g. of the anilide and 10 cc. of 100% hydrazine hydrate was heated on the steam-bath for five minutes. A nearly clear solution rapidly formed, then the product began to separate. The mixture was diluted with water and the product removed; yield, 720 mg. (65%), m.p. 193–195°. A similar preparation was obtained as a white solid, m.p. 195–197°, and was analyzed.

Anal. Calc'd for $C_{23}H_{29}N_5O_3S$: N, 15.4. Found: N, 15.4.

The yield of hydrazide varied from 60–80% depending upon the purity of the uracil anilide, X.

2-(δ-Carbanilidobutyl)-4-carbanilido-5-ketoimidazolido[4,5,c,cis]thiophane (XII). To a hot solution of 720 mg. of 2-(δ-carbanilidobutyl)-3-uranilinothiophane-*cis*-4-carboxhydrazide (XI) in 7.2 cc. of dry butanol containing 85 mg. of dry hydrogen chloride was added 0.21 cc. of butyl nitrite. The solution, although gas evolution was complete in five minutes, was heated on the steam-bath for thirty minutes, then evaporated to dryness *in vacuo*. The residue was heated to boiling with 10 cc. of methanol, then cooled in an ice-bath. After several hours, the product was collected and washed with cold methanol; yield, 310 mg. (45%), m.p. 169–173°. An additional 110 mg. (16%), m.p. 170–173°, separated from the filtrate after standing for one week at −3°. Recrystallization from dilute alcohol gave white crystals, m.p. 173–174°.

Anal. Calc'd for $C_{23}H_{26}N_4O_3S$: C, 63.0; H, 6.0; N, 12.8.
Found: C, 62.8; H, 6.3; N, 12.9, 13.1.

Attempted diazotization of the hydrazide, XI, in 0.5 *N* hydrochloric acid with sodium nitrite failed to give any of the desired product.

epi-2-(δ-Carboxybutyl)-3,4-cis-diaminothiophane sulfate (XIII). A mixture of 380 mg. of 2-(δ-carbanilidobutyl)-4-carbanilido-5-ketoimidazolido[4,5,c,*cis*]thiophane (XII), 2 g. of barium hydroxide octahydrate, and 5 cc. of 50% methanol was shaken in a bomb at 170–180° for twenty hours. The product was isolated in the same manner as described for the diamine derived from *dl*-biotin (1); yield, 210 mg. (77%), m.p. 240–250°dec. For analysis a sample was recrystallized from aqueous methanol, white crystals, m.p. 244–245°dec.

Anal. Calc'd for $C_9H_{20}N_2O_6S_2$: C, 34.2; H, 6.4.
Found: C, 34.2; H, 6.3.

epi-2-(δ-Carboxybutyl)-5-ketoimidazolido[4,5,c,cis]thiophane (dl-epibiotin) (XIV). A solution of 180 mg. of *epi*-2-(δ-carboxybutyl)-3,4-*cis*-diaminothiophane sulfate (XIII) in 16 cc. of 10% sodium carbonate was treated with phosgene with ice cooling until acidic. The product separated slowly in two hours at 0°; yield, 110 mg. (79%) of white crystals, m.p. 190–191°. After several days the filtrate deposited an additional 15 mg. (11%), m.p. 190–191°. Recrystallization from water, in which it is much more soluble hot than *dl*-biotin, gave long white needles of the same m.p.

Anal. Calc'd for $C_{10}H_{16}N_2O_3S$: C, 49.2; H, 6.6; N, 11.5.
Found: C, 49.4; H, 7.2; N, 11.5.

Desulfurization with Raney nickel gave *dl*-desthiobiotin, m.p. 160–161° (2). A mixture with an authentic sample of *dl*-desthiobiotin prepared by the desulfurization of *dl*-biotin gave no depression in m.p. The identity of the desulfurized product was also demonstrated by its biotin activity (6), being 50% as active as biotin when assayed by the yeast method.

SUMMARY

The synthesis of *dl-epi*biotin, a previously unknown isomer of *dl*-biotin, has been described and the stereochemistry of its method of preparation discussed.

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BIOTIN. VIII. PENTHIANE-3,4-DICARBOXYLIC ACID

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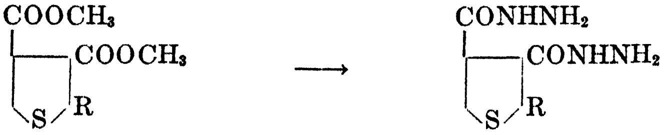
It was recently demonstrated (1) that treatment of a 2-alkylthiophane-3,4-*cis*-dicarboxylic ester (I) with hydrazine resulted in the formation of a 2-alkylthiophane-3,4-*trans*-dicarboxhydrazide (II), inversion of configuration having taken place. As carbocyclic *cis*-diesters form dihydrazides with retention of configuration (2), it seemed of interest to investigate whether inversion in this reaction was limited to the thiophane nucleus, *cf.* I, or was a property of sulfur containing rings in general. It has now been found that the penthiane nucleus, *cf.* X, behaves in an analogous fashion.



cis
I

trans
II

3-Carbethoxy-4-ketopenthiane (III) (3), when treated with hydrogen cyanide gave a cyanohydrin, IV, which could be dehydrated with phosphorus oxychloride and pyridine to 3-carbethoxy-4-cyano-Δ^3-penthiene (V). Acid hydrolysis of the latter failed to form the unsaturated diacid, VI, but resulted in a polymeric product. Acid hydrolysis of the cyanohydrin, IV, (R = Me or Et) proceeded smoothly to a mixture of stereoisomeric 4-hydroxypenthiane-3,4-dicarboxylic acids (VII), which was dehydrated with acetic anhydride in excellent yield to Δ^3-penthiene-3,4-dicarboxylic anhydride (VIII). The crystalline anhydride, on reduction with sodium amalgam in aqueous alkali, gave a mixture of the *cis* and *trans* forms of penthiane-3,4-dicarboxylic acid (IX).

The pure *trans*-diacid was obtained by esterifying the *cis-trans* mixture and treatment with methanolic sodium methoxide followed by alkaline hydrolysis. The *cis*-diacid, IX a, was obtained from this same mixture by boiling with propionic anhydride, distillation, and hydrolysis of the *cis*-anhydride.

When heated with hydrazine, both the *cis* and *trans*-3,4-dicarbomethoxypenthianes (X) gave the same dihydrazide, XI. That the latter had the *trans* configuration was demonstrated by acid hydrolysis back to *trans*-penthiane-3,4-dicarboxylic acid (IX b).

Curtius degradation of *trans*-penthiane-3,4-dicarboxhydrazide (XI) to the *trans*-diurethan, XII, and subsequent hydrolysis with hydrobromic acid resulted in *trans*-3,4-diaminopenthiane dihydrobromide (XIII), characterized as its dicarbamido derivative (XIV) and dibenzoate (XV).

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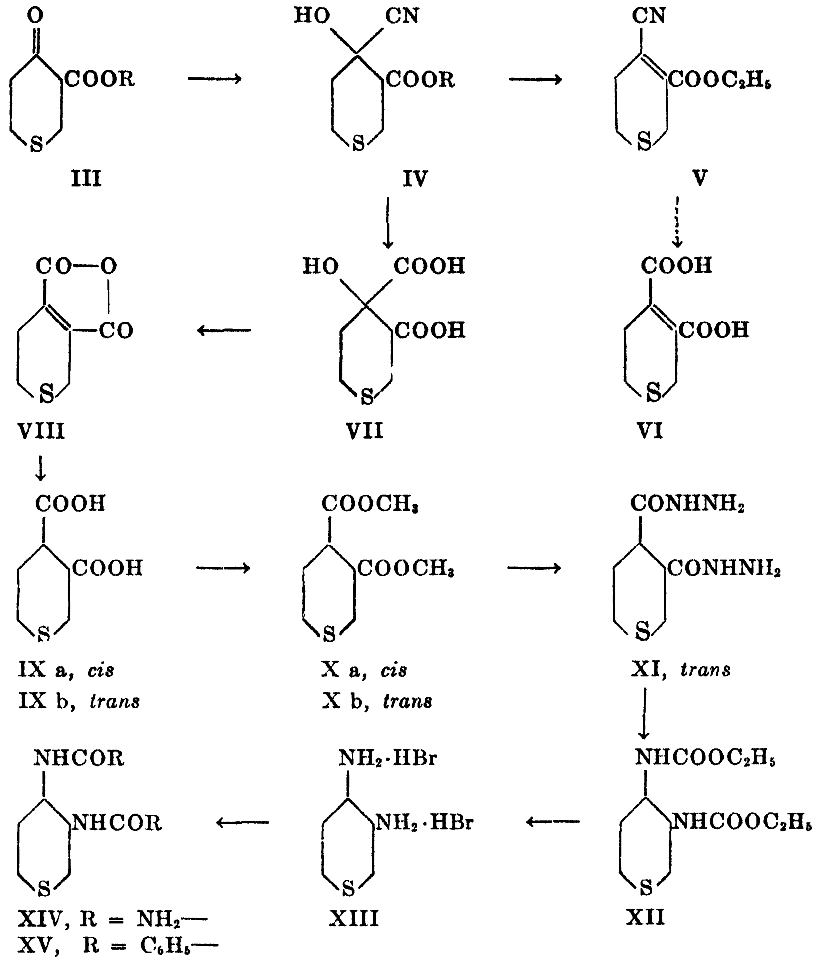
of the intermediates, and Louis Brancone and Louis Dorfman for the microanalyses.



EXPERIMENTAL

3-Carbethoxy-4-ketopenthiane (III). This compound was prepared by Dieckmann cyclization of ethyl β,β'-thiodipropionate in 32–35% yield according to the method of Bennett and Scorah (3). The corresponding methyl ester was obtained in 28% yield, b.p. 134–136° (12 mm.) and solidified after a few days.

Anal. Calc'd for $C_7H_{10}O_3S$: C, 48.2; H, 5.7.

Found: C, 47.8; H, 5.1.

3-Carbethoxy-4-cyano-Δ^3-penthiene (V). To a mixture of 8.2 g. of 3-carbethoxy-4-ketopenthiane (III) and 8 cc. of liquid hydrogen cyanide cooled in an ice-bath was added 0.1 cc. of 50% potassium hydroxide. After fifteen hours at 0°, the mixture was acidified with 0.7 cc. of 85% phosphoric acid and the excess hydrogen cyanide removed *in vacuo*. The residual cyanohydrin, IV, dissolved in 30 cc. of benzene and decanted from the syrupy phosphates, was treated with 37 cc. of dry pyridine and 4 cc. of phosphorus oxychloride. The heat of reaction maintained a temperature of 42° for one hour. After being refluxed for two hours, the mixture was poured into iced hydrochloric acid and ether. The separated organic layer was washed successively two times each with cold 3 *N* hydrochloric acid, cold 3% potassium hydroxide and finally water. After removal of the solvent, the residue was distilled, yellow oil, b.p. 125–128° (1 mm.); yield, 6.2 g. (74%).

Anal. Calc'd for $C_9H_{11}NO_2S$: N, 7.1. Found: N, 7.4.

Hydrolysis of the cyano ester, V, with a boiling mixture of hydrochloric and acetic acids gave anomalous results. The glassy product appeared to be polymeric in nature instead of the diacid, VI, as it failed to distil when converted to the methyl ester and it was unaffected by sodium amalgam in dilute alkali.

4-Hydroxypenthiane-3,4-dicarboxylic acid (VII). 3-Carbethoxy-4-ketopenthiane (III) (8.2 g.) was converted to the cyanohydrin, IV, as described above. The latter was refluxed for nineteen hours with 16 cc. of acetic acid and 40 cc. of concentrated hydrochloric acid. After evaporation to dryness *in vacuo*, the mixture was diluted with 30 cc. of water twice and evaporated to dryness each time. The residue was extracted with acetone and filtered from ammonium chloride. The filtrate was again evaporated to dryness *in vacuo*. The residual mixture of isomers was an amber gum; yield, 10.0 g. (99%).

Anal. Calc'd for $C_7H_{10}O_5S$: C, 40.7; H, 4.9.
Found: C, 40.3; H, 4.7.

In larger runs it was necessary to add the keto ester in portions to the hydrogen cyanide and potassium hydroxide in order to keep the temperature from rising above 15°.

Δ^3-*Penthiene-3,4-dicarboxylic anhydride (VIII).* A mixture of 131 g. of crude 4-hydroxypenthiane-3,4-dicarboxylic acid (VII) and 650 cc. of acetic anhydride was refluxed for two and one-half hours, then evaporated to dryness *in vacuo*. The residue, dissolved in chloroform, was filtered through Celite to remove some insoluble tarry material, the solvent removed and the residue distilled, b.p. 134–136° (1 mm.); yield, 96 g. (94% based on the original keto ester, III). The distillate solidified in the receiver and was purified for analysis by recrystallization from benzene-petroleum ether; cream colored crystals, m.p. 82–83°.

Anal. Calc'd for $C_7H_6O_3S$: C, 49.3; H, 3.5.
Found: C, 49.1; H, 3.1.

cis- and trans-Penthiane-3,4-dicarboxylic acid. (IX). A solution of 95 g. of Δ^3-penthiene-3,4-dicarboxylic anhydride (VIII) in 820 cc. of 5% sodium hydroxide was stirred with 1550 g. of 2% sodium amalgam at 80° for two hours. After decantation from the mercury, the solution was strongly acidified, saturated with salt, and extracted with ethyl acetate (6 l., in several portions. The combined extracts, dried with anhydrous magnesium sulfate were evaporated to dryness *in vacuo*. The semi-crystalline residue weighed 92 g. (87%) and was used without further purification. For analysis a sample was recrystallized from acetone-benzene, white crystals, m.p. 154–160°.

Anal. Calc'd for $C_7H_{10}O_4S$: C, 44.2; H, 5.3.
Found: C, 43.8; H, 5.6.

Esterification by the continuous drying method (1) using chloroform, methanol, and sulfuric acid gave the dimethyl ester, X, as a nearly colorless oil, b.p. 155–159° (12 mm.).

trans-Penthiane-3,4-dicarboxylic acid (IX b). A solution of 3.5 g. of *cis-* and *trans*-3,4-dicarbomethoxypenthiane (X) in 10 cc. of methanol containing 50 mg. of sodium was refluxed for two and one-half hours to invert the *cis* ester present to *trans*. To one-half of the solution was added 1.5 g. of potassium hydroxide. After being refluxed for about ten minutes, a crystalline potassium salt began to separate, which was dissolved by the addition of 3 cc of water. The solution was refluxed for two hours, acidified, saturated with salt, and extracted several times with ethyl acetate. The dried extracts on evaporation *in vacuo* gave 1.5 g. of crystals which were recrystallized from acetone-benzene, m.p. 173–178°; yield, 1.1 g. (72%). Several more recrystallizations gave white crystals, m.p. 175 5–177°.

Anal. Calc'd for $C_7H_{10}O_4S$: C, 44.2; H, 5.3.
Found: C, 44 6; H, 5.8.

cis-Penthiane-3,4-dicarboxylic acid (IX a). A solution of 11 g. of *cis-* and *trans*-penthiane-3,4-dicarboxylic acid (IX) in 57 cc. of propionic anhydride was refluxed for two hours. The excess propionic anhydride was removed *in vacuo* and the residue distilled. The orange distillate of somewhat impure *cis*-penthiane-3,4-dicarboxylic anhydride boiled at 122–128° (1 mm.); yield, 5 g. (49%).

Anal. Calc'd for $C_7H_8O_3S$: C, 48.8; H, 4.7.
Found: C, 50.0; H, 4.6.

The anhydride was heated on the steam-bath with excess dilute sodium hydroxide for thirty minutes. The solution was acidified, saturated with salt and extracted several times with ethyl acetate. The dried extracts were evaporated and the residue recrystallized from acetone-benzene, white crystals, m.p. 166–167.5°; yield, 0.7 g. Further recrystallization raised the m.p. to 167–168°. A mixture with *trans*-penthiane-3,4-dicarboxylic acid (IX b) melted at 159–160°.

Anal. Calc'd for $C_7H_{10}O_4S$: C, 44.2; H, 5.3.
Found: C, 44.6; H, 4.7.

trans-Penthiane-3,4-dicarboxhydrazide (XI). (A). A mixture of 1.75 g. of the *cis* and *trans* isomers of 3,4-dicarbomethoxypenthiane (X) was converted to the *trans* ester as described under *trans*-penthiane-3,4-dicarboxylic acid. To the methanol solution was added 1.5 cc. of 85% hydrazine hydrate. After being refluxed for ninety minutes, the mixture was cooled and the product removed; yield, 1.2 g. (69%). Recrystallization from 60% propanol gave white needles, m.p. 206–208°.

Anal. Calc'd for $C_7H_{14}N_4O_2S$: C, 38.5; H, 6.5; N, 25.7.
Found: C, 38.4; H, 6.2; N, 25.8.

A solution of 0.5 g. of the above hydrazide in 6 *N* hydrochloric acid was heated on the steam-bath for one hour. Extraction with ethyl acetate and evaporation gave the free acid which was recrystallized from acetone-benzene; white crystals, m.p. 175–177°. The m.p. was not depressed on admixture with *trans*-penthiane-3,4-dicarboxylic acid (IX b), but depressed to 154–159° when mixed with the *cis* acid (m.p. 166–167°) (IX a).

(B). The *cis*-3,4-dicarbomethoxypenthiane (X a) prepared from 70 mg. of pure *cis*-diacid (IX a) and an excess of ethereal diazomethane was refluxed one hour with a little methanol containing excess hydrazine hydrate. The product which separated on cooling melted at 204–206° alone or when mixed with *trans*-penthiane-3,4-dicarboxhydrazide (XI).

trans-3,4-Dicarbethoxyaminopenthiane (XII). To a solution of 7.5 g. of *trans*-penthiane-3,4-dicarboxhydrazide (XI) in 97 cc. of 1 *N* hydrochloric acid was added 100 cc. chloroform. The mixture was stirred in an ice-bath and treated dropwise with 4.7 g. of sodium nitrite in 30 cc. of water over a period of one hour. After being stirred at 0° for an additional thirty minutes, the mixture was separated and the aqueous layer extracted with chloroform. The combined chloroform solutions were dried with calcium chloride at 0° for twenty minutes, then diluted with 75 cc. of absolute ethanol and refluxed for one hour. After removal of the solvent the residue was recrystallized from ethanol to give 4.0 g., m.p. 172–173°, and 2.0 g., m.p. 165–168°, of white crystals (total 63%).

Anal. Calc'd for $C_{11}H_{20}N_2O_4S$: C, 47.8; H, 7.3; N, 10.1.
Found: C, 47.7; H, 6.9; N, 10.3.

When the sodium nitrite was added over a period of ten minutes, the yield dropped to about 25% and much free nitrous acid was evolved.

trans-3,4-Diaminopenthiane dihydrobromide (XIII). A mixture of 0.75 g. of *trans*-3,4-dicarbethoxyaminopenthiane (XII) and 7 cc. of 48% hydrobromic acid was refluxed for ten minutes, when solution was complete. It was clarified with Norit and cooled to 5°. The dihydrobromide formed white crystals, m.p. 295° dec.; yield, 0.7 g. (88%).

Anal. Calc'd for $C_5H_{14}Br_2N_2S$: C, 20.4; H, 4.8; N, 9.5.
Found: C, 20.3; H, 4.7; N, 9.3.

trans-3,4-Dicarbamidopenthiane (XIV). A solution of 100 mg. of *trans*-3,4-diaminopenthiane dihydrobromide (XIII) and 100 mg. of potassium cyanate in 3 cc. of water was allowed to stand for several hours. The white crystals which separated were recrystallized from water, m.p. 248°; yield, 50 mg. (67%).

Anal. Calc'd for $C_7H_{14}N_4O_2S$: C, 38.5; H, 6.5; N, 25.7.
Found: C, 39.0; H, 6.2; N, 25.6.

trans3-,4-Dibenzoylaminopenthiane (XV). This compound was prepared from benzoyl chloride and *trans*-3,4-diaminopenthiane dihydrobromide (XIII) by the usual Schotten-Baumann procedure. It was purified by recrystallization from pyridine, white crystals, m.p. 314–316°.

Anal. Calc'd for $C_{19}H_{20}N_2O_2S$: C, 67.1; H, 5.9; N, 8.2.
Found: C, 66.7; H, 5.8; N, 8.1.

SUMMARY

The *cis* and *trans* forms of penthiane-3,4-dicarboxylic acid have been synthesized and characterized.

cis-3,4-Dicarbomethoxypenthiane, when treated with hydrazine, gave *trans*-penthiane-3,4-dicarboxhydrazide. An inversion of configuration took place in the same manner as in the analogous thiophane series.

Several derivatives of *trans*-3,4-diaminopenthiane have been described.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

CONDENSATION OF AROMATIC ALDEHYDES WITH α-PICOLINE METHIODIDE

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Styryl derivatives of pyridine and quinoline and their methiodides can serve as useful intermediates in the preparation of types of compounds known to possess valuable pharmacological properties. Some of the methiodides are known to be powerful photosensitizers for light of certain wave lengths. A series of 2-styrylpyridine methiodides has been made for pharmacological examination, and some correlations have been noted between the colors of the products, the yields obtained, and the substituents on the nucleus of the aldehyde reactants.

It has long been recognized that substituents in the 2 or 4 position of pyridine and quinoline rings were subject to the same type of activation as occurs with similar substituents when located either ortho or para to nitro groups on a benzene ring. Thus 2- or 4-methylpyridines or quinolines, or *o*- or *p*-nitrotoluenes can be made to condense with aromatic aldehydes to give stilbene-like products. These condensations usually require strenuous dehydrating conditions and frequently give poor yields. Kaufmann and Vallette (1) reported the observation that the methiodides of these methylpyridines and quinolines react more readily and under milder reaction conditions than the tertiary bases. Thus, although no condensation was obtained between *p*-nitrosodimethylaniline and quinaldine, lepidine, or α-picoline by heating at elevated temperatures, the methiodides of the heterocyclic bases reacted with the nitroso compound rapidly in alcohol solution, even at room temperature, piperidine being used as a condensing agent.

Recently Koelsch (2) reported the preparation of four α-stilbazole methiodides and summarized the few instances of prior work in this line. Koelsch condensed his aldehyde reactants with equimolecular amounts of α-picoline methiodide in alcohol solution at room temperature with a trace of piperidine as catalyst.

In this work, the preparative procedure chosen was a modification of that of Koelsch. An excess of aromatic aldehyde (1½ to 2 moles of aldehyde per mole of α-picoline methiodide) was used to make it more likely that any unreacted starting material would be the aldehyde, as this should be more readily separable from the salt-like product than α-picoline methiodide. The catalyst piperidine was used in larger amounts (about ½ mole piperidine per mole of α-picoline methiodide) and the reaction mixtures were refluxed for periods of from one to four hours. Repetition of some of Koelsch's preparations under our conditions led to greater yields more rapidly obtained.

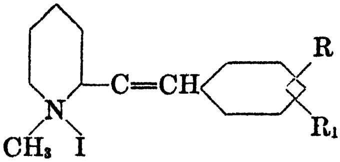
EXPERIMENTAL

All melting points are uncorrected.

Preparation of the stilbazole methiodides. Five grams (0.021 *M*) of α-picoline methiodide and 5 g. (0.03–0.04 *M*) of the aldehyde to be condensed were mixed and dissolved in 25–30

TABLE I

DERIVATIVES OF α-Stilbazole METHIODIDE



COMP'D NO.	SUBSTITUENTS ON BENZENE RING	M.P., °C.	YIELD %	ANALYSIS				ABSORPTION MAXIMUM, Å
				Calc'd		Found		
				C	H	C	H	
I	None[a]	230–231	73	52.00	4.37	51.95	4.45	3340[b]
II	4-CH_3	263–264	65	53.40	4.78	53.33	4.60	
III	2-Cl-	228–229	63	46.98	3.66	47.10	3.66	
IV	3-Cl-	293–294	72	46.98	3.66	47.00	3.81	
V	3-NO_2-[c]	258–260	85	45.64	3.56	45.56	3.76	
VI	4-CH_3O-[c]	242–243	92	50.98	4.57	50.70	4.34	3590[b]
VII	2-HO-	253–254	82	49.54	4.16	49.60	4.38	
VIII	3-HO-	221–222	92	49.54	4.16	49.49	3.90	
IX	4-HO-[c]	269–270	70	49.54	4.16	49.29	3.88	3630[b] 4350[d]
X	3,4-CH_2O_2	295	70	49.03	3.84	49.08	4.02	
XI	3,4-$(CH_3O\text{-})_2$	244–245	88	50.12	4.72	50.23	4.89	
XII	2,5-$(CH_3O\text{-})_2$	244–245	88	50.12	4.72	50.29	4.96	3270[b]
XIII	3-CH_3O-4-HO-	275–276	83	48.77	4.36	48.77	4.61	
XIV	3-C_2H_5O-4-HO-	260–261	88	50.12	4.72	50.08	4.99	
XV	2-HO-3-C_2H_5O-	242–243	83	50.12	4.72	50.20	4.88	
XVI	3,4-$(HO\text{-})_2$	270–271	40	47.31	3.97	47.60	4.58	
XVII	4-$(CH_3)_2N$-[e]	273–274	97	52.43	5.24	52.48	5.20	4440[b] 3230[f]
XVIII	4-$(CH_3)_3N$-[g] I	272–273	67	40.14	4.37	39.93	4.31	3200[b]
XIX	3-Br-4-$(CH_3)_2N$-	232–233	73	43.13	4.09	42.94	3.99	3600[b]
XX	4-$(C_2H_5)_2N$-	246–247	95	54.79	5.88	54.68	6.05	

[a] Koenigs, Köhler, and Blindow [*Ber.*, **58**, 933 (1925)] have reported this compound, but give its melting point as 215–216°.

[b] Absorption spectrum of a 0.0013% solution in distilled water.

[c] Previously described by Koelsch, reference (2).

[d] Absorption spectrum of 0.00066% solution in 0.1 *N* sodium hydroxide.

[e] Previously described by Mills and Pope, reference (5).

[f] Absorption spectrum of 0.00066% solution in 0.1 *N* hydrochloric acid.

[g] This product made in two ways as described in text. The yield reported here is that obtained from reaction of the quaternary iodide of the aldehyde with α-picoline methiodide.

cc. of absolute methanol. Piperidine (1 cc.) was added and the reaction mixture was refluxed on the steam-bath for a period of from one to four hours, or until bumping from precipitated solid became prohibitive. After cooling, the solid was collected, washed with and recrystallized from methanol. In a number of cases, the results of which are the basis for some discussion, preparations were run in duplicate. Yields reported are those of product crystallized once from methanol. Sometimes the first crop of crystals obtained from the reaction mixture represented only a fraction of the total yield, and in these cases the mother liquors were evaporated to a small volume to obtain a second crop. The combined crops were then recrystallized from methanol to obtain the reported yield. The results are shown in Table I.

Alternative preparation of XVIII. p-Dimethylamino-α-styrylpyridine methiodide (XVII) (1.2 g.) was mixed with 5 cc. of methyl iodide in 25 cc. of methanol and the mixture was refluxed for 10 hours. Partial evaporation of the solvent, followed by cooling, yielded 1.0 g. (50–60%) of yellow-orange crystals. After crystallization from methanol the product melted at 272–273°, and was identical with the material obtained from condensation of α-picoline methiodide with the methiodide of *p*-dimethylaminobenzaldehyde. The melting of this compound seems to involve a gradual reversion to the more stable structure XVII by the loss of methyl iodide, for the color undergoes a change from yellow-orange to deep red as the temperature is raised, and the final melting point, with decomposition, is identical with that of XVII.

Absorption spectra. Absorption spectra of a few of the representative types were taken to give a more precise basis for some of the discussion. The absorption curves for these compounds are very much the same in general shape, showing intense absorption in the ultraviolet and one characteristic peak, varying in intensity and exact location with the individual compounds, but lying in or near the visible portion of the spectrum.

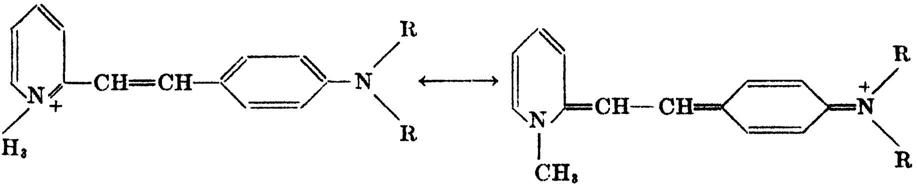
The absorption maxima of compounds I (3340 Å), XII (3270 Å), XVII in acid solution (3230 Å), and XVIII (3200 Å) were taken as a rough indication of the probable location of the maxima for most of the other substituted compounds, which would not be expected to possess the more powerful resonance effects.

Acknowledgment. The author is happy to express his gratitude to Mr. Samuel W. Blackman for the analytical results reported here, to Mr. Walter S. Ide for the absorption spectra obtained, and to Dr. Richard Baltzly for his continued interest and advice.

DISCUSSION

A. *Color.* As would be predicted on the basis of the theory of color outlined by Lewis and Calvin (3), the α-stilbazole methiodides were colored, though except for the dialkylamino compounds all were of varying shades of yellow. The *p*-dimethylamino and *p*-diethylamino derivatives, however, were a bright purple-red color. This marked deepening of color with the latter compounds is attributed to the increase in intensity of light absorption and the displacement of the absorption maxima to longer wave lengths consequent upon the greater mobility of electrons of the chromophoric system stimulated by the additional important contribution of resonance forms of type A(b) to the classical structure A(a).

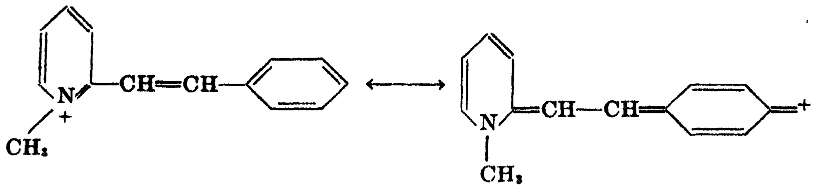
A



(a) XVII R = CH_3
XX R = C_2H_5
(bright red; R = CH_3 abs. max. 4440 Å)

(b)

I



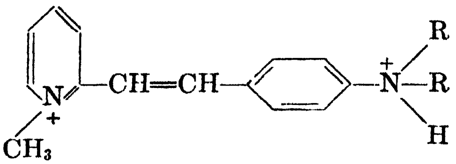
(a) (b)

(yellow; abs. max. 3340 Å)

Resonance forms of the type I(b) should differ widely in energy content from the classical structure I(a), and thus would be expected to contribute relatively weakly to the total structure of the molecule, or to its light absorption characteristics.

The energy contents of the resonance forms A(a) and A(b) should be much more nearly equal, and A(b) would therefore be expected to participate to a much greater extent in the over-all structure of the molecule. In harmony with both theory and facts, the presence of the strong basic auxochrome facilitates and intensifies the absorption of light as compared with the unsubstituted molecule I.

That resonance forms of the type shown in A(b) are important in color production in the molecule is indicated by the fact that the addition of dilute hydrochloric acid to the highly colored compound, in water, produces a colorless solution. When the *p*-dialkylamino group on the benzene ring is tied up as the hydrochloride A(c), the valence requirements of this nitrogen are completely fulfilled, and having no unshared electron pairs it can no longer enter into important resonance structures such as A(b). Addition of alkali restores the original deep red color.

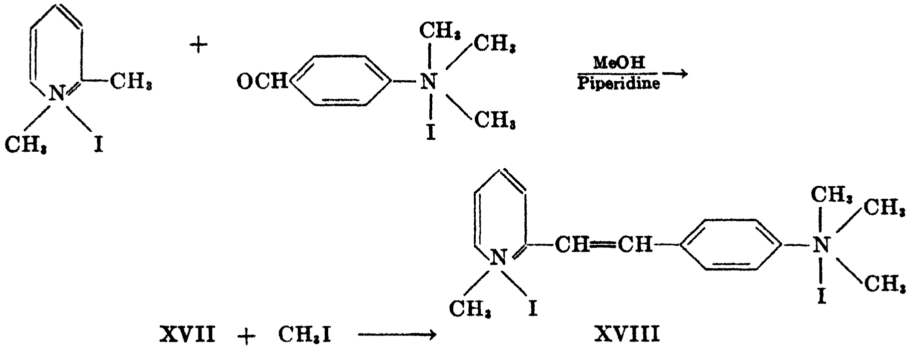


A. (c)

(colorless; R = CH_3, abs. max. 3230 Å)

Two other methods were used to test the hypothesis that interference with the resonance forms A(b) would decrease or destroy the color of the molecule:

(I) The bis-methiodide XVIII corresponding to XVII was made by two methods:

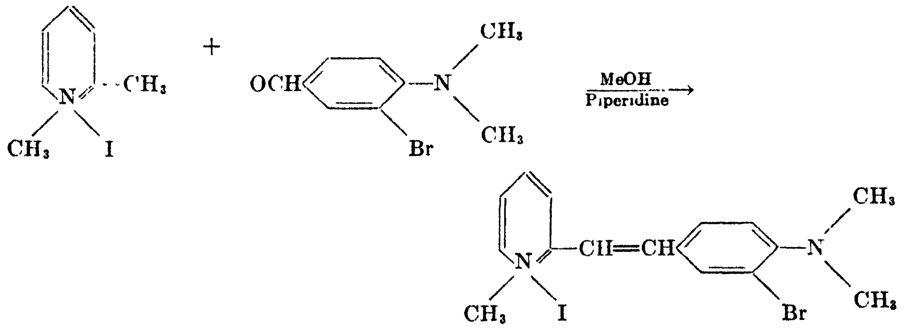


XVII + CH_3I ⟶ XVIII

(pale yellow; abs. max. 3200 Å)

In this case, as with the hydrochloride A(c), the *p*-nitrogen on the phenyl is saturated, in the form of its quaternary salt, and can no longer give rise to such structures as A(b). The product XVIII has a pale yellow color with its characteristic absorption maximum at 3200 Å as compared with the maximum at 4440 Å for compound XVII. Its maximum lies at significantly shorter wave lengths even than that of I (3340 Å), and this can be explained, possibly, as the repression of the weak resonance forms of type I(b) by the presence of the strong cation in the para position of the benzene ring.

(II) Introduction of a large atom or group into one or both of the positions adjacent to the dimethylamino group should, by steric hindrance, mechanically interfere with the coplanarity of the dimethylamino group and the benzene ring, thereby cutting down or eliminating completely the participation of the A(b) type of resonance.



XIX

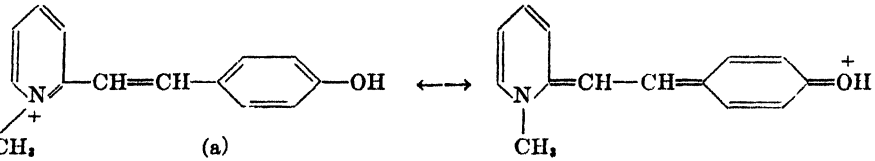
(light orange; abs. max. 3600 Å)

Bromination of *p*-dimethylaminobenzaldehyde gave *m*-bromo-*p*-dimethylaminobenzaldehyde, which upon condensation with α-picoline methiodide gave XIX. This product was light orange in color (abs. max. 3600 Å) indicating that by the device being tested here resonance of the A(b) type is inhibited considerably but not completely eliminated.

Cocker and Turner (4) have prepared the *m*-dimethylamino- and *m*-diethylamino-stilbazole methiodides and described them as orange or orange-red crystals, giving orange colored solutions. They also report the discharge of the color of their products by acids and restoration by alkali. Thus, dialkylamino groups, even in the meta position, can serve as auxochromic groups, although the A(b) resonance structures are not possible for them. Since the absorption data are not available, it is impossible to compare precisely the positions and intensities of the maxima for these substances with those of XVII. But from the color description afforded one might place the absorption maxima of the *m*-derivatives at about 3600–3800 Å. Certainly from theoretical considerations the characteristic maxima should fall at markedly shorter wave lengths than for the para analogs. Also the shift in the position of the maxima for the meta compounds, on addition of acid, should cover a much narrower range than with the para derivatives. More evidence may be presented on this point at a later date.

The hydroxystilbazole methiodides offer another good opportunity for the correlation of color with the possibility of important resonating ionic structures.

IX

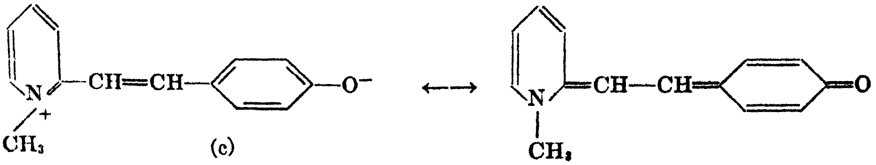


(yellow; abs. max. 3630 Å) (b)

When the hydroxyl group if located in the *o*- or *p*- positions resonance forms such as IX(b) can be written. However, the energy contents of the (a) and (b) forms of IX should not be as nearly the same as were the (a) and (b) forms of A. Thus, the contributions to the structure and color of the molecule should be much less with IX(b) than was the case with A(b). In agreement with these expectations the hydroxystilbazoles were all pale yellow and for IX the absorption maximum was at 3630 Å.

In alkaline solution, however, other resonance forms are possible [IX(c) and IX(d)] in which the energy contents of the two principal resonating structures should be more nearly the same and these forms should be of marked influence on the color and structure of the compound.

IX



(deep red; abs. max. 4350 Å) (d)

All the 2- or 4-hydroxystilbazole methiodides gave pale yellow or colorless solutions in water or alcohol. Addition of alkali produced deep red solutions, presumably through the effect of the important resonating structures of type IX(c) and IX(d). Acidification restored the original colorless, or nearly colorless, state.

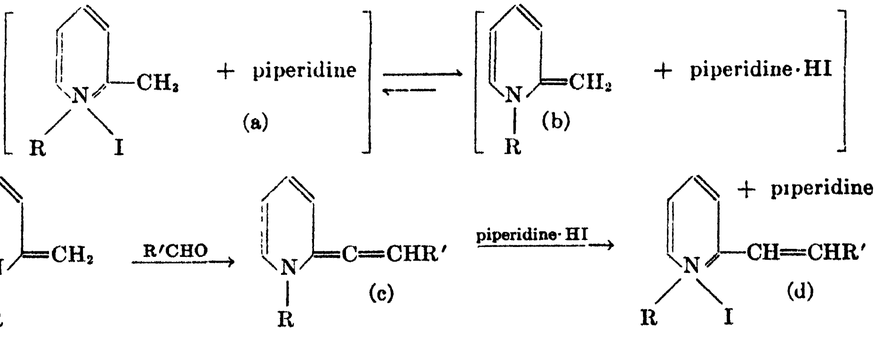
The 3-hydroxy derivatives, as would be predicted from the impossibility of attaining the structures postulated for the 2- and 4-derivatives, are pale yellow in color and show no visible color change in the presence of alkali.

B. *Yields.* In general the yields were very good in the reaction being examined,varying between 70–100%. Yields obtained in any individual case were reproducible within about ± 2% under the same conditions. The most surprising result was the excellent yields obtained with the *p*-dialkylaminobenzaldehydes, as *p*-dimethylaminobenzaldehyde is usually considered to be exceptionally unreactive. In the present condensation, however, the *p*-dimethylamino and *p*-diethylamino aldehydes gave results significantly better than any of the other aldehydes used. This observation was made doubly significant, since in various other reactions typical of aromatic aldehydes, these two either fail to react or give markedly poorer yields than most of the others.

The *p*-dimethylaminostilbazole methiodide had been made by Mills and Pope (5), who described its brilliant color characteristics and behavior towards acids, but made no statement of the yield obtained.

Before discussing the relationship between the yields obtained and resonance structure it is significant to point out the mechanism of this reaction as elucidated by Mills and Raper (6). They suggested the mechanism shown in B below:

B



According to them, in a mixture containing the α-picoline methiodide, piperidine, and an aromatic aldehyde, the first reaction would involve the abstraction of hydrogen iodide from the α-picoline methiodide by the stronger base piperidine to give piperidine hydriodide and some of the methylene base. The methylene base being extremely reactive would then combine with the aldehyde to form the allene base, which, finally, being a stronger base than either the methylene base or piperidine, reacts with piperidine hydriodide liberating piperidine and forming the stilbazole methiodide.

Now since most of the methylene or allene bases of pyridine or quinoline would be very reactive compounds, either liquid or low-melting, it should be extremely difficult to isolate or purify them. But Mills and Raper (6) by using β-naphthaquinaldine alkiodides (methyl and ethyl) succeeded in isolating, purifying, and analyzing every member of the series of steps indicated in B, and showed that each behaved in the manner indicated. Thus the naphthaquinaldine methiodide with piperidine gave a crystalline solid methylene base; this, in turn, reacted rapidly with *p*-dimethylaminobenzaldehyde, in the absence of condensing agent, to give the allene derivative; and this, finally, reacted with either hydrogen iodide or piperidine hydriodide to give the *p*-dimethylaminostyryl methiodide derivative (plus free piperidine in the latter case) identical with that obtained from the direct condensation of β-naphthaquinaldine methiodide with *p*-dimethylaminobenzaldehyde by means of piperidine.

Now the critical step for the correlation between resonance structure and yield, in this reaction, would be the one between B(c) and piperidine hydriodide. For the effective base strength of the allene intermediate should be directly related to the degree of increased stability attained by transformation into the resonating ion through acquisition of hydrogen iodide from the hydriodide of the powerful base piperidine. And the yield obtained should be directly proportional to the base strength of the allene, since the strength of this as a base would determine the extent to which the final step of the series of reactions (B) would proceed.

In the allenes, resonance between the two rings is effectively blocked and these compounds are consequently highly reactive and unstable. By the addition of hydrogen iodide, resonance between the two rings is again possible, making the methiodides so formed more stable, less reactive substances. The powerful tendency to change from the unstable, reactive allene structure to the quaternary salts, stabilized by additional resonance between the rings, makes the allenes the strong bases they are. The strength of this basicity should be in direct proportion to the extent of the resonance between the rings.

Theory and facts are again in agreement, for in the cases where it would be predicted that resonance factors would be most powerful [A(a) and A(b)], it has been shown that light absorption is most intense, color deepest, and yield greatest. These facts have been shown to be true by comparison with a case [I(a) and I(b)] where resonance factors should play a relatively minor role. Thus yields for compounds XVII and XX were 97% and 95% respectively as compared with 73% for I. Also various modifications of structure have been made with the most powerful resonator XVII, with the intent to cut down the amount of resonance possible. The effect of this blocking of resonance on the color of the products has already been discussed, but the diminutions in color were likewise paralleled by diminutions in yields. Compounds XVIII and XIX were obtained in yields of 67% and 73% respectively, while their close relative XVII was obtained in 97%.

Next below the most powerful dialkylaminostilbazole methiodides with regard to importance of resonance effects should be the 4-hydroxy and 4-methoxy derivatives. For these the resonance effects should be considerably less powerful than with the dialkylamino analogs, but more powerful than the other substituted derivatives. Compounds VI and IX had absorption maxima at 3590 Å and 3630 Å compared with 3340 Å for I and 4440 Å for XVII. Also VI was obtained in 92% yield compared with 73% for I. The poor yield, 70%, of IX obtained is explicable through the fact that the most important resonance structures for this molecule [IX(c) and IX(d)] would lend to hinder or render difficult the isolation of the substance having the classical structure IX(a) under the basic reaction conditions used in this condensation.

No attempt will be made to labor through probably meaningless interpretations of the minor variations in yields (between 70–85%) of the other substituted derivatives, because no clear cut pattern is to be expected. For with many of the other substituents the electronic effects are apt to be much less powerful, more ambiguous, and perhaps overshadowed by a number of different factors such as steric hindrance, or solubility.

SUMMARY

A series of α-stilbazole methiodides has been prepared. It has been observed in this series, that when the products can be written as resonating ions in which major contributions to ion stability could reasonably be expected from the styryl portion of the molecule, these products were obtained in exceptionally good yields and were highly colored compounds. Introduction of factors calculated to block the resonance contribution of the styryl moiety resulted in marked diminution in both color and yields of products.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

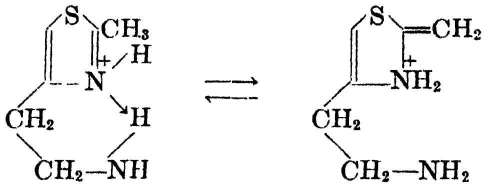
ANALGESIC STUDIES. β-ETHYL AND β-ISOPROPYLAMINE DERIVATIVES OF PYRIDINE AND THIAZOLE[1]

ALFRED BURGER AND GLENN E. ULLYOT

Received November 5, 1946

In comparing the three isomeric β-pyridylethylamines, Niemann and Hays (1) observed that the 2-isomer exhibited histamine-type activity, while the 3- and 4-isomers had an epinephrine-like effect. They explained the absence of histamine action in these two amines on the basis of the postulate that the ion of only the 2-isomer could exist in a form in which both the heterocyclic and the aliphatic nitrogen atoms participated in a chelated ring. Since β-arylethylamine derivatives show, in general, a less prolonged physiological effect than branched-chain amines of corresponding structure, we decided to synthesize several β-pyridylisopropylamines in order to explore the effect of branching on the activity of such compounds. As the work progressed it became desirable to include examples of the isosteric β-thiazolylethylamine series for further comparison.

In the course of testing β-(2-methyl-4-thiazolyl)ethylamine (I) Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School, observed that this compound exhibited considerable analgesia in rats. We considered it possible that the methyl group in the reactive 2-position may tautomerize, and that the ionized amine then reacts to some extent as represented by I (b). This form would have less tendency to exhibit chelation than β-(4-thiazolyl)ethylamine,[2] and the tautomerizable methyl group could thus be held responsible for a decrease of histamine activity in this compound.



I(a) I(b)

In order to support this assumption, β-(2-pyridyl)isopropylamine and β-(6-methyl-2-pyridyl)isopropylamine were tested. The former showed an appreciable histamine-like action, while the latter was practically devoid of this effect and was found to have an analgesic action in cats. It should be observed that β-(2-aryl-4-thiazolyl)ethylamines have been shown to possess a high degree of "physiological activity" (3); β-(2-benzyl-4-thiazolyl)ethylamine described in this article had no analgesic properties.

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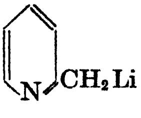
[1] Several experiments reported in this article were performed by G. E. U. in the Research Laboratories of Smith, Kline, and French Laboratories.

[2] This can be corroborated by an inspection of Stuart models of the two tautomers. After conclusion of most of this work we learned of the article by Erlenmeyer and Müller (2) who mentioned β-(4-thiazolyl)ethylamine "was qualitatively similar to histamine in its type of activity."

β-(2-Pyridyl)isopropylamine (IV) was prepared by the Leuckart reaction from 2-pyridylacetone (III) which, in turn, was obtained by interaction of 2-picolyllithium (II) and acetonitrile with subsequent hydrolysis of the resulting ketimine. While the synthesis of 2-pyridylacetone and its 6-methyl homolog produced acceptable yields, certain other homologs could not be obtained in a very satisfactory manner by this route. 2-Methyl-5-ethylpyridine furnished 22% of (5-ethyl-2-pyridyl)acetone, and 2-*n*-amylpyridine only 10% of 3-(2-pyridyl)heptanone-2. However, the conversion of these ketones to the corresponding primary amines was readily accomplished.



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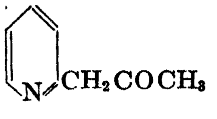
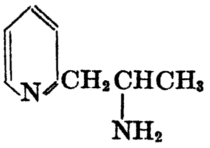


III

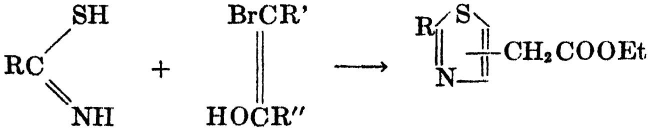


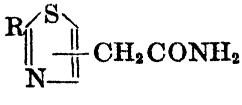
IV

Metal exchange of γ-picoline with phenyllithium seemed to take a normal course but treatment of the lithium derivative with acetonitrile or with acetyl chloride and subsequent hydrolysis, failed to give a ketonic product. 2,4-Lutidine also furnished a non-ketonic compound under the same conditions.

Several attempts to prepare β-(3-pyridyl)isopropylamine were unsuccessful. Contrary to expectation (4), pure 1-nicotinyl-1-isonitrosoethane (5) absorbed only two moles of hydrogen under the conditions of the Rosenmund and Karg reduction, which has been applied by the authors of this reaction to the reduction of isonitroso ketones to primary amines.

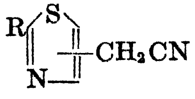
The synthesis of most of the β-thiazolylethylamines (X) followed, on the whole, the pattern set by Price and Pickel (6) in their preparation of β-(4-methyl-5-thiazolyl)ethylamine. The necessary bromo keto esters (V) were condensed with thioamides (VI), the resulting ethyl thiazolylacetates (VII) were converted to the nitriles (IX) through the amides (VIII), and the acetonitrile derivatives were hydrogenated to the amines (X). In the reactions leading to thiazoles unsubstituted in position-2, formamide and phosphorus pentasulfide could be used (7) but they proceeded more uniformly when this mixture was replaced by thioformamide.

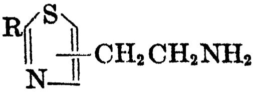




VI V VII VIII

R′ or R″ may be —CH_2COOEt





IX X

The dehydration of the amides to the nitriles went best under the influence of phosphorus oxychloride. Difficulties encountered in the dehydration of thiazole-4-acetamide were overcome by modifying the standard procedure. The hydrogenation of the nitriles was accomplished in the presence of Raney nickel catalyst, if necessary at elevated pressures. However, the catalytic hydrogenation of thiazole-4-acetonitrile did not go satisfactorily for us even though various conditions and catalysts were tried. On the other hand, Erlenmeyer and Müller (2) did not mention any difficulty in this reduction in their report of the synthesis of β-(4-thiazolyl)ethylamine. We had begun an alternative synthesis (XI–XIV) but did not complete it after reading the paper of the Swiss authors.

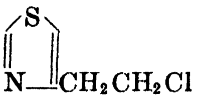
β-Chloropropionyl chloride (XI) was converted to 1-bromo-4-chlorobutanone-2 (XII) *via* the diazo ketone, and the bromo ketone was condensed with thioformamide to yield β-(4-thiazolyl)ethyl chloride (XIII). The phthalimido compound XIV prepared next was hard to hydrolyze, and this approach was interrupted at this point.

$ClCH_2CH_2COCl$

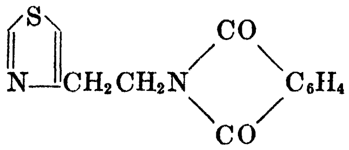
XI

$ClCH_2CH_2COCH_2Br$

XII



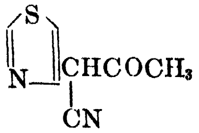
XIII



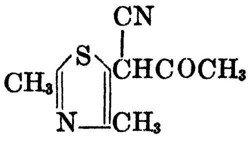
XIV

The effect of N-alkylation of the primary amino group in an analgesically active ethylamine derivative was tested in the case of β-(2-methyl-4-thiazolyl)-benzylethylamine. This secondary amine did not exhibit any of the analgesic activity observed in the primary amine (I) from which it was prepared through the benzal derivative.

For a contemplated synthesis of β-thiazolylisopropylamines the corresponding thiazolyl acetone derivatives were needed as intermediates. Their preparation from thiazolyl acetonitrile derivatives and methylmagnesium halides proved unsuitable because of excessive formation of tars. Condensation of the acetonitriles with ethyl acetate was successful in two cases, but the cyano ketones thus obtained (XV) and (XVI) yielded only the corresponding thiazolyl acetonitrile derivatives on acid cleavage.



XV



XVI

EXPERIMENTAL[3]

2-Pyridylacetone. This ketone was prepared from α-picolyllithium and acetonitrile by a method developed independently by us but which was essentially that described by Ruigh (8). The yield was around 35%. See the details for the preparation of 6-methyl-2-pyridylacetone.

β-(2-Pyridyl)isopropylamine. A solution of 69 g. (0.51 mole) of 2-pyridylacetone in 52 g. of 85% formic acid was added dropwise to 112.5 g. (2.5 moles) of formamide in an apparatus set for downward distillation, and with the reaction flask in an oil-bath heated to 160–180°. After the addition was completed, heating was continued for five hours, water and other low-boiling materials were removed under reduced pressure up to 84° (8 mm.), and the remaining liquid was cooled and treated with two 100-cc. portions of concentrated hydrochloric acid. Some ammonium chloride precipitated; the mixture was heated on a steam-bath for one hour, cooled, made strongly alkaline, and distilled with steam. Two liters of clear distillate was collected, made strongly alkaline by addition of solid sodium hydroxide, and the precipitated oil was separated. The aqueous layer was extracted several times with ether and benzene, the extracts were combined with the oil, and dried over potassium hydroxide. Fractionation of the dried solution yielded 42 cc. (about 60%) of a colorless oil, b.p. (12 mm.) 96.5–97°. The boiling point reported in the literature (9) is 103–104° (13 mm.).

No crystalline hydrochlorides or sulfates of the base could be obtained.

6-Methyl-2-pyridylacetone. To a suspension of 13 g. of lithium in 400 cc. of dry ether, stirred mechanically under an atmosphere of nitrogen, was added a solution of 147 g. of dry bromobenzene in 200 cc. of ether over a period of two hours. After the spontaneous refluxing had subsided, stirring and boiling was maintained for another three hours. A solution of 100 g. of pure 2,6-lutidine in 100 cc. of ether was dropped in without external heating. The mixture turned orange-red and boiled. It was refluxed for two hours, and allowed to stand under nitrogen overnight. A solution of 39 g. of dry acetonitrile in 100 cc. of ether was added slowly to the stirred and slightly warmed mixture. Mild refluxing and a lightening of the color were observed. After another four to five hours' boiling, the mixture was poured onto 500 g. of crushed ice, and neutralized and hydrolyzed with a mixture of 350 g. of ice and 350 cc. of 35% hydrochloric acid with external cooling and stirring. The ether layer was separated, the acid solution washed with ether, cooled, and made alkaline with an ice-cold solution of 200 g. of sodium hydroxide in 300 cc. of water. The alkaline mixture was extracted with six portions of ether, the ether extract was dried over sodium sulfate, filtered, and evaporated. The residue was fractionated, yielding as the main portion a yellow oil weighing 71 g., b.p. 96–98° (0.5 mm.), 114–115° (9.5–10 mm.), 119–120° (16 mm.). From the foreruns, another 8 g. of the ketone was obtained.

The *picrate* crystallized from ethanol as yellow needles, m.p. 136–137.5°.

Anal. Calc'd for $C_{15}H_{14}N_4O_8$: C, 47.62; H, 3.73; N, 14.81.
Found: C, 47.98; H, 3.61; N, 14.77.

The *semicarbazone* was prepared from the ketone and a neutral semicarbazide solution in aqueous alcohol. After removal of the alcohol, colorless needles separated which, after two recrystallizations from dilute ethanol, appeared as shining crystals, m.p. 144–144.5°.

Anal. Calc'd for $C_{10}H_{14}N_4O$: N, 27.17. Found: N, 26.79.

β-(6-Methyl-2-pyridyl)isopropylamine. The Leuckart reaction was performed on the whole as described for the lower homolog. A solution of 28 g. of 6-methyl-2-pyridylacetone in 20.8 g. of 88% formic acid, and 44.8 g. of formamide were used. The crude amine was extracted from the reaction mixture without previous steam distillation. The fraction of b.p. 72° (0.5 mm.), 78–82° (1-1 5 mm.), 94° (4.5 mm.), 95° (5 mm.), 112–113° (14–15 mm.), weighed 13.7 g. and consisted of a colorless oil of strong amine odor.

The *dihydrochloride* was prepared in acetone-ether solution, recrystallized from methanol, and washed with acetone. The colorless crystals melted at 213.5–215° and were slightly hygroscopic.

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[3] All melting points are corrected. Microanalyses by Miss Lillian Sillano and Mrs. Gertrude Carney of Smith, Kline, and French Laboratories

Anal. Calc'd for $C_9H_{14}N_2 \cdot 2HCl$: Cl, 31.78. Found: Cl, 31.67.

3-(2-Pyridyl)-2-heptanone. Phenyllithium, prepared from 7 g. of lithium dust and 80 g. of bromobenzene in 450 cc. of dry ether, was treated with 75 g. of 2-*n*-amylpyridine[4] and then with acetonitrile as described in the preparation of 6-methyl-2-pyridylacetone. Besides much unchanged starting material (34 g.) and high-boiling fractions, 17 g. of a yellow oil, b.p. 138–142° (4 mm.) was obtained. It yielded a *semicarbazone* which crystallized as colorless crystals from dilute alcohol, m.p. 126–126.5°.

Anal. Calc'd for $C_{13}H_{20}N_4O$: N, 22.57. Found: N, 22.35, 22.44.

1-Amino-2-methyl-3-(2-pyridyl)hexane. The Leuckart reaction with 17 g. of 3-(2-pyridyl)heptanone-2, 12.5 g. of formic acid, and 27 g. of formamide yielded 9 g. of an almost colorless oil, b.p. 129–130° (2.5 mm.), 152–154° (4–5 mm.) which turned pale brown on standing and was not obtained in a completely pure state. The hydrochloride, picrate, sulfate, and phenylurea could not be crystallized.

Anal. Calc'd for $C_{12}H_{20}N_2O$: Neut. equiv., 192.3. Found: 201.3, 200.0.

(5-Ethyl-2-pyridyl)acetone. One hundred grams of 2-methyl-5-ethylpyridine[5] was allowed to react with phenyllithium prepared from 14.7 g. of lithium dust and 185 g. of bromobenzene, and then treated with 70 g. (100% excess) of acetonitrile. The mixture was worked up as usual, and the oily reaction product fractionated. A considerable amount of unchanged starting material was recovered; the ketonic fraction (36 g.) boiled at 90–130° (1.5 mm.), mostly at 112–113°. Two refractionations yielded 22 g. of pale yellow oil, b.p. 95° (0.3 mm.). It was converted to the *picrate*, and the long yellow needles of the salt were recrystallized from acetone-ethanol to the constant melting point 108–109.5°.

Anal. Calc'd for $C_{16}H_{16}N_4O_8$: N, 14.28. Found: N, 14.38, 14.45.

β-(5-Ethyl-2-pyridyl)isopropylamine. This compound was prepared by the Leuckart reaction using 44 g. of (5-ethyl-2-pyridyl)acetone, 32.4 g. of formic acid, and 70 g. of formamide. The yield of the amine, b.p. 100° (1.5 mm.), was 12 g. The colorless oily base did not give a solid hydrochloride. The *picrate* crystallized from acetone or ethanol as long yellow needles, m.p. 222–224° (dec.).

Anal. Calc'd for $C_{16}H_{19}N_5O_7$: N, 17.81. Found: N, 18.08, 17.91.

Ethyl γ-bromoacetoacetate. The directions of Conrad (10) were modified in the following manner.

To an ice-cold solution of 600 g. of ethyl acetoacetate in 750 cc. of dry ether, 741 g. of bromine was added dropwise in the course of 90 minutes with vigorous shaking and good cooling. Hydrogen bromide was evolved during the addition. After standing at room temperature for 24 hours, the mixture was decomposed with 600 g. of ice, washed with a sodium carbonate solution saturated with sodium chloride, to alkaline reaction, and finally with saturated sodium chloride solution. The ether layer was dried over calcium chloride with shaking for one day, the solvent removed under reduced pressure on a water-bath, and the cooled residual oil stabilized immediately by addition of 2–3 g. of barium carbonate. The reddish lachrymatory oil may be kept in a dark bottle for several days. The yield in several runs varied from 510 to 825 g. Attempts to distill the crude brominated ester under greatly diminished pressure resulted in considerable decomposition with evolution of hydrogen bromide. Moreover, the colorless distillate did not furnish appreciably better yields in thiazole ring closures than the crude material.

The red bicarbonate-alkaline extract of the crude reaction mixture contained small amounts of a highly lachrymatory oil, probably ethyl α-bromoacetoacetate, which could be liberated by acidifying the solution.

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[4] Purchased from Reilly Tar and Chemical Corporation and redistilled, b.p. 208–209° (753 mm.).

[5] Kindly supplied by Dr. Robert Frank, University of Illinois.

Ethyl 4-thiazolylacetate. (a) A mixture of 400 g. of crude ethyl γ-bromoacetoacetate, 400 g. of dry benzene, 80 g. of formamide, and 80 g. of (practical grade) phosphorus pentasulfide was shaken vigorously for one to two and one-half hours until it became warm spontaneously. The flask was immersed in cold water with continued shaking, and the temperature was not permitted to rise above 50°. The exothermic condensation lasted about 90 minutes, and the yellow phosphorus pentasulfide turned to a reddish tar. The mixture was then allowed to stand for 18 to 24 hours, and decomposed with 1075 cc. of 0.75 N hydrochloric acid. The large quantity of brown resins was filtered, the two layers in the filtrate were separated, and the acid solution was washed several times with ether. It was then cleared with Darco, made alkaline with solid sodium carbonate, and extracted with ten portions of ether. The combined ether extracts were washed with saturated sodium chloride solution, dried over sodium sulfate for at least one day, and filtered through Darco in order to remove some tar which settled out slowly. The solvent was removed, and the oily residue fractionated. The colorless ester boiled at 111° (2 mm.), 116° (6 mm.), 138–140° (30 mm.), or 160° (71 mm.) and smelled slightly of pyridine. The best yield obtained in eight analogous condensations was 60 g., but the average was 35 g.

If the temperature was allowed to rise above 50° during the condensation it became hard to control the reaction. In one instance cooling was delayed too long, and the solvent boiled out explosively. In another, the reaction was so slow to start that the flask was warmed on a steam-bath; although it was set in an ice-bath as soon as the reaction began, the reaction could not be controlled.

The *picrate* of the ester crystallized from ethanol or methanol; the pale yellow needles melted at 109–110°. A recent article (11) records this melting point at 112°.

Anal. Calc'd for $C_{13}H_{12}N_4O_9S$: N, 14.00. Found: N, 14.16.

(b) Our second method, used independently, is so similar to that recently described by Jones, Robinson, and Strachan (11) that we wish to forego a detailed description. The thioformamide used was kindly supplied by Dr. C. C. Christman, then of Merck & Company, Elkton, Virginia. The yields in several runs were essentially those obtained by the British authors.

4-Thiazolylacetamide. A mixture of 198 g. of ethyl 4-thiazolylacetate and 600 cc. of 20% ammonium hydroxide was shaken overnight, the clear solution evaporated under reduced pressure or under an air-jet, and the semi-solid residue treated with some dioxane. The crystalline amide was filtered and recrystallized from dioxane. By working up the mother liquors, additional quantities of the amide were obtained, a total of 132.5 g. (74%). In another run, 55 g. of the ester yielded 48 g. (98%) of the amide. The colorless plates melted at 123–123.5°.

Anal. Calc'd for $C_5H_6N_2OS$: N, 19.70. Found: N, 19.83.

4-Thiazolylacetonitrile. Fifty grams of finely powdered 4-thiazolylacetamide was added in several portions to 300 cc. of phosphorus oxychloride contained in a 1-liter flask cooled in water. The mixture now contained large lumps of material and was shaken mechanically for 72 hours. The fine pale brown powder was filtered, washed with some phosphorus oxychloride, and placed in a flask containing 500 g. of fresh phosphorus oxychloride. This mixture was boiled under reflux for two hours until all the solid had gone into solution. This could be facilitated by crushing larger lumps with a glass rod, or by adding some sodium chloride which, by mechanical action, broke up the lumps. The yield of the nitrile was not affected by the addition of sodium chloride. The dark clear solution thus obtained, and the phosphorus oxychloride filtrate from the original treatment of the amide, were worked up separately in a similar manner.

Excess phosphorus oxychloride was removed under reduced pressure, the brown viscous residue decomposed carefully with chipped ice, and the solution filtered from tar through a layer of Darco. At this point, the two acid solutions were combined, and made distinctly alkaline with sodium bicarbonate. Much sodium phosphate, and some tar precipitated. After filtration, the precipitate was washed well with ether and discarded. The filtrate was extracted exhaustively with ether, the ether extract dried over sodium sulfate, the solvent removed on a steam-bath, and the oily residue fractionated. The colorless distillate boiled at 97–98° (2 mm.) or 110° (5 mm.), $n_D^{28.5}$ 1.5391. The yield was 81%. This contrasts with the 40–50% obtained by Erlenmeyer and Müller (2) by dehydration with phosphorus pentoxide.

Anal. Calc'd for $C_5H_4N_2S$: C, 48.37; H, 3.25.
Found: C, 48.26; H, 3.75.

The *picrate* crystallized from ethanol as yellow needles, m.p. 107.5–108.5°.

Anal. Calc'd for $C_{11}H_7N_5O_7S$: N, 19.83. Found: N, 19.86.

α-(4-Thiazolyl)-α-cyanoacetone. To 7.2 g. of sodium dust dispersed in 200 cc. of hot xylene by rapid stirring under an atmosphere of nitrogen, 40 cc. (about 1.5 moles) of absolute ethanol was dropped slowly without further external heating. After the spontaneous boiling had subsided, the mixture was stirred for another twenty minutes, cooled to 40°, and a mixture of 30 g. of 4-thiazolylacetonitrile, 32 g. of ethyl acetate freshly distilled over phosphorus pentoxide, and 500 cc. of absolute ether was added dropwise. Occasional cooling was necessary to keep the temperature at 30–40°. The color of the mixture changed to orange-yellow, and the sodium salt of the cyano ketone precipitated out. After stirring rapidly for another 90 minutes, 100 cc. of dry ether was added to complete the precipitation of the sodium salt. The salt was filtered, washed with ether, dissolved in 200 cc. of water, and the solution extracted with ether. It was then acidified slowly with acetic acid, and made ammoniacal. The precipitated oil was extracted with six portions of ether, the extracts were dried over sodium sulfate, the solvent was evaporated, and the dark oil was distilled. It boiled at 140° (1–2 mm.), and the colorless distillate solidified in the receiver to crystals weighing 23.7 g (59%). Recrystallization from dilute methanol yielded prisms or needles, m.p. 65.5–67.5°.

Anal. Calc'd for $C_7H_6N_2OS$: N, 16.93. Found: N, 16.86.

Hydrolysis of α-(4-thiazolyl)-α-cyanoacetone. A suspension of three grams of the cyano ketone in 21 cc. of 15% sulfuric acid was boiled under reflux for 7.5 hours; the material steam-distilled into the condenser, and then dissolved slowly as hydrolysis proceeded. The cooled solution was made alkaline with sodium carbonate and extracted five times with ether. The residual oil from the dried ether solution was converted to a picrate which melted at 103–105°; a mixture melting point with 4-thiazolylacetonitrile picrate (m.p. 107–108°) was 106–107°. The oily reaction product gave no semicarbazone.

1-Bromo-4-chlorobutanone-2. Eighty grams of β-chloropropionyl chloride was dropped into a stirred solution of diazomethane (from 215 g. of nitrosomethylurea) in 3 l. of methylene chloride at −5° over a period of forty minutes. After the vigorous evolution of nitrogen had slowed down, the solution was allowed to stand at room temperature overnight. It was then cooled to 0°, stirred rapidly, and 90 cc. of 48% hydrobromic acid added gradually. Stirring was continued for several hours, anhydrous sodium carbonate was then added to neutralize excess hydrogen bromide, the methylene chloride layer was separated, dried over calcium chloride, and the solvent distilled, the last portions being removed under reduced pressure. The vacuum distillation of the solvent was interrupted as soon as the bromo ketone turned dark; the lachrymatory oil weighed 80 g. and was not purified further.

β-(4-Thiazolyl)ethyl chloride.[6] Commercial thioformamide was diluted with twice its volume of water, and extracted into several portions of ether. The solvent was distilled under reduced pressure, and the pale brown oil used immediately.

Eighty grams of crude 1-bromo-4-chlorobutanone-2 was dissolved in 100 cc. of absolute ethanol, the stirred solution cooled to − 5°, and 54 g. of thioformamide, dissolved in 54 cc. of ethanol, dropped in over a period of one hour, the temperature being kept below 0°. Careful cooling was necessary especially towards the end of the period when the temperature tended to rise considerably. After standing at 4° for two days the solution was concentrated under diminished pressure, the dark tarry residue was diluted with 100 cc. of 0.1 *N* hydrochloric acid, and filtered through filter pulp and charcoal. The slightly turbid filtrate was made alkaline with sodium bicarbonate, and extracted with six 100-cc. portions of ether. The yellow ether solution was dried over potassium carbonate, and the solvent distilled in a vacuum. The residual oil was converted to the picrate in ethanol solution. The crude picrate weighed 79.5 g. (49%, based on the bromo ketone). It was recrystallized by dissolving it in a small volume of hot acetone, adding an excess of absolute ethanol, and boiling off the acetone. The picrate was very sparingly soluble in ethanol and crystallized on cooling. The yellow needles melted at 134°.

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[6] Prepared with the assistance of Mr. R. E. Ferebee.

Anal. Calc'd for $C_{11}H_9ClN_4O_7S$: C, 35.07; H, 2.41; N, 14.87.
Found: C, 35.52; H, 2.69; N, 14.53.

The base was liberated by dissolving the picrate in 75 cc. of an 8% lithium hydroxide (12) solution and extracting exhaustively into ether. The ether extract was placed over anhydrous potassium carbonate which both dried the solution and precipitated some potassium picrate. The solution was cleared with Darco, filtered, and the ether distilled, the last 100 cc. being removed in a vacuum. The oily β-(4-thiazolyl)ethyl chloride (20 g.) was immediately condensed with potassium phthalimide.

2-(4-Thiazolyl)-N-phthalimidoethane. Condensation of 20 g. of the oily 2-(4-thiazolyl)-ethyl chloride just described with 40 g. of potassium phthalimide in 200 cc. of decalin at 180–190° with stirring for nine hours, filtration from insoluble material, and removal of the decalin *in vacuo* resulted in a dark residue weighing 2.5 g. which crystallized from ethanol. Recrystallization from dilute ethanol furnished colorless needles, m.p. 99–100° (after slight sintering).

Anal. Calc'd for $C_{13}H_{10}N_2O_2S$: N, 10.85. Found: N, 10.70.

Ethyl (2-methyl-4-thiazolyl)acetate was prepared from thioacetamide and ethyl γ-bromoacetoacetate by the method of Steude (13) without isolation of its hydrobromide. The colorless ester boiled at 138–140° (20 mm.) or 165° (31 mm.). The yields, in several batches, varied from 23 to 41%.

The *hydrochloride* of the ester crystallized slowly from acetone. Recrystallized from methanol-ether, the colorless prisms melted at 184–186° (decomp.).

Anal. Calc'd for $C_8H_{11}NO_2S{\cdot}HCl$: N, 6.32. Found: N, 6.54.

2-Methyl-4-thiazolylacetamide. Fifty-seven grams of ethyl 2-methyl-4-thiazolylacetate was shaken with 165 cc. of 20% ammonium hydroxide overnight, the dark clear solution filtered rapidly with some charcoal, and the amide allowed to crystallize from the filtrate. The long, colorless octagonal plates were washed with a little ammonium hydroxide. They were practically pure; recrystallization from dioxane led to the m.p. 139–140°. By concentrating and purifying the mother liquors, a total yield of 42 g. was obtained.

Anal. Calc'd for $C_6H_8N_2OS$: N, 17.94. Found: N, 18.29, 18.38.

2-Methyl-4-thiazolylacetonitrile. A mixture of 38 g. of 2-methyl-4-thiazolylacetamide and 250 cc. of freshly distilled phosphorus oxychloride was refluxed gently for 90 minutes. The solid amide melted to a brown oil which gradually went into solution; after a few minutes, crystals separated out but went back into solution in the course of the heating. Excess phosphorus oxychloride was removed at 60° and 35 mm. pressure, the residue was decomposed with crushed ice, and the cooled solution was made strongly alkaline with sodium carbonate. The mixture was extracted with three portions of ether, the ether layer was washed with water and filtered with the aid of Darco. The clear, almost colorless solution was dried over sodium sulfate, the solvent was removed on a steam-bath, and the oily nitrile distilled at 143° (26 mm.) or 104–105° (3 mm.) as a colorless oil, n_D^{25} 1.5252. The yield was 92%.

The *picrate* crystallized from ethanol as hard yellow prisms, m.p. 104–106°.

Anal. Calc'd for $C_{12}H_9N_5O_7S$: N, 19.07 Found: N, 19.63.

β-(2-Methyl-4-thiazolyl)ethylamine. A solution of 44 g. of 2-methyl-4-thiazolylacetonitrile in 440 cc. of saturated ethanolic ammonia was mixed with 20 g. of Raney nickel catalyst, and hydrogenated at an initial pressure of 75 atmospheres. Absorption began at 110°, and was completed at 120–130° overnight. The catalyst was filtered with the aid of Darco, the filtrate concentrated in a vacuum at 90°, and the dark oil fractionated. At 82–83° (2–3 mm.), or 78° (1 mm.), 19 g. of a colorless oil distilled, n_D^{25} 1.5350. Its *picrate* crystallized as long yellow needles from ethanol, m.p. 209–211° (decomp.).

Anal. Calc'd for $C_{12}H_{13}N_5O_7S$: N, 18.86. Found: N, 19.05.

Besides the primary amine, a viscous greenish fraction of b.p. 150–210° (2 mm.) was also obtained. It was converted to the picrate, and the salt recrystallized from much ethanol. The broad golden-yellow needles melted at 148–149.5° and appeared to be di-β-(2-methyl-4-thiazolyl)ethylamine picrate.

Anal. Calc'd for $C_{18}H_{20}N_6O_7S_2$: N, 16.93. Found: N, 16.99.

The base was liberated from the pure picrate, dried over potassium hydroxide, and the almost colorless oil converted to the hydrochloride in acetone-ether solution. After recrystallization from methanol-acetone the colorless, water-soluble crystals melted at 205–207°; yield, 1 g.

Anal. Calc'd for $C_{12}H_{17}N_3S_2 \cdot 3HCl$: N, 11.15. Found: 10.89.

In another batch, hydrogenation of the nitrile proceeded rapidly under ordinary pressure at 25°. The yield of primary amine was 75%. However, in several other runs, high pressures had to be employed.

β-(2-Methyl-4-thiazolyl)ethylbenzalimine. A solution of 19 g. of β-(2-methyl-4-thiazolyl)-ethylamine in 20 cc. of absolute ethanol was dropped into an ice-cold solution of 14 g. of freshly distilled benzaldehyde in 28 cc. of absolute ethanol. After standing at room temperature for 48 hours the pale yellow solution was concentrated at 15 mm. and 70°, and the oily residue fractionated. Besides 9 g. of unchanged primary amine, a fraction boiling at 163° (2 mm.) was obtained in a yield of 28.5 g. The colorless oil was redistilled and exhibited b.p. 152–154° (1 mm.), n_D^{20} 1.5885.

The *dipicrate* crystallized as fine yellow needles from a small volume of ethanol; m.p. 129–130°.

Anal. Calc'd for $C_{25}H_{20}N_8O_{14}S$: N, 16.31. Found: N, 16.94.

β-(2-Methyl-4-thiazolyl)ethylbenzylamine. A solution of 28.5 g. of freshly distilled β-(2-methyl-4-thiazolyl)ethylbenzalimine in 400 cc. of absolute ethanol was hydrogenated in the presence of 10 g. of Raney nickel catalyst at 90° and 75 atmospheres of hydrogen for one day. After filtering the catalyst, the almost colorless solution was concentrated at 20 mm. pressure, and the oily residue fractionated. After a small forerun, 22.2 g. (77.4%) of a colorless oil boiled at 154–155° (1–2 mm.); n_D^{27} 1.5668. It was converted to its *dihydrochloride* in acetone solution, and the salt recrystallized from methanol-ether. The colorless leaflets melted at 186–189° (evacuated tube) after sintering at 183°.

Anal. Calc'd for $C_{13}H_{16}N_2S \cdot 2HCl$: Cl, 23.23. Found: Cl, 23.02, 23.01.

The *picrate* crystallized from ethanol. The yellow needles melted at 165.5—167.5°.

Anal. Calc'd for $C_{13}H_{16}N_2S \cdot C_6H_3N_3O_7$: N, 15.18. Found: N, 14.86, 14.90.

Ethyl (2,4-dimethyl-5-thiazolyl)acetate. A solution of 65 g. of thioacetamide in 260 cc. of absolute ethanol was cooled to −3°, and 140 g. of ethyl β-bromolevulinate, dissolved in 140 cc. of absolute ethanol, dropped in over a period of one hour with occasional shaking. After four hours at −3°, the mixture was kept at 4° overnight, and at 25° for 36 hours. The solvent was distilled at 40° and 20 mm., the pale yellow residue dissolved in 500 cc. of 0.1 *N* hydrochloric acid, and extracted with ether. The acid solution was made alkaline with sodium bicarbonate and extracted with four portions of ether. The ether extract was dried over sodium sulfate, filtered, the solvent distilled, and the pale yellow oil fractionated. The colorless fraction boiling at 150° (18 mm.) weighed 91 g. (78%) and showed n_D^{24} 1.5115. It turned yellow on standing.

The *picrate* crystallized from ethanol as yellow blades, m.p. 109.5–111°.

Anal. Calc'd for $C_{15}H_{16}N_4O_9S$: N, 13.08. Found: N, 13.11.

2,4-Dimethylthiazole-5-acetic acid. A solution of 20 g. of the ester and 6.5 g. of potassium hydroxide in 100 g. of methanol was refluxed for three hours, the solvent removed under reduced pressure, the yellow residue dissolved in water and neutralized to *p*H 6.5. The acid crystallized after a few minutes. After completing the crystallization overnight, the material was filtered, dried in the air, recrystallized from a little ethanol, and washed with ethyl acetate and finally with ether. The yield of colorless crystals melting at 183–184° was 18 g.

Anal. Calc'd for $C_7H_9NO_2S$: N, 8.18. Found: N, 8.37.

2,4-Dimethyl-5-thiazolylacetamide. This amide was prepared from the ester with ammonium hydroxide in the usual manner. It crystallized from the reaction mixture in almost pure form in a yield of 82%. Recrystallization from a little ethanol rendered colorless felted needles, m.p. 174–175.5°.

Anal. Calc'd for $C_7H_{10}N_2OS$: N, 16.45. Found: N, 16.69.

2,4-Dimethyl-5-thiazolylacetonitrile. Forty-two grams of 2,4-dimethyl-5-thiazolylacetamide was mixed slowly with 420 cc. of phosphorus oxychloride, and the mixture heated to boiling. The amide turned oily and went into solution, but a crystalline precipitate appeared soon which, in turn, went into solution in the course of the reaction. After 75 minutes, the excess phosphorus oxychloride was distilled under reduced pressure, the dark viscous residue was decomposed with 500 g. of ice, the brown solution was filtered with Darco, and made alkaline with sodium carbonate. The nitrile precipitated as a brown oil which crystallized soon; the yield, augmented by some additional material obtained by extraction of the alkaline mother liquors with benzene, was 64%. Purification by distillation at 123° (2.5 mm.) yielded a colorless distillate which solidified in the receiver. It was recrystallized from dilute ethanol, the resulting colorless prisms melting at 87–88°.

Anal. Calc'd for $C_7H_8N_2S$: N, 18.41. Found: N, 18.38.

The *picrate* crystallized from ethanol as shining yellow leaflets, m.p. 122.5–124°.

Anal. Calc'd for $C_{13}H_{11}N_5O_7S$: N, 18.37. Found: N, 18.46.

β-(2,4-Dimethyl-5-thiazolyl)ethylamine. A solution of 23 g. of 2,4-dimethyl-5-thiazolylacetonitrile in 460 cc. of absolute ethanol was hydrogenated in the presence of 12 g. of Raney nickel catalyst under atmospheric pressure. Almost all the required hydrogen was absorbed within a few hours. The catalyst was filtered with Darco, the pale yellow filtrate concentrated in a vacuum, and the residue distilled. Nine grams of colorless distillate, b.p. 84° (2 mm.), n_D^{20} 1.5358 was collected.

The *dipicrate* crystallized from ethanol and melted at 189–190°.

Anal. Calc'd for $C_{19}H_{18}N_8O_{14}S$. N, 18.24. Found: N, 18.97, 18.95.

α-(2,4-Dimethyl-5-thiazolyl)-α-cyanoacetone. A mechanically stirred suspension of 22.4 g. of sodium methoxide in 500 cc. of absolute ether was treated, under an atmosphere of dry nitrogen, with a mixture of 56 g. of 2,4-dimethylthiazolyl-5-acetonitrile and 35 g. of dry ethyl acetate in 700 cc. of ether. When, after the dropwise addition of 50 cc. of this mixture, and refluxing for fifteen minutes, no reaction was observed, 10 cc. of absolute ethanol was added. The color changed immediately to a reddish purple. The remainder of the reagents was now added over a period of 45 minutes while the sodium enolate separated as a pale tan powder. Refluxing was continued for another five and one-half hours, and 5 g. of ethyl acetate and 5 cc. of absolute ethanol were added in portions. The slurry became somewhat thicker; the precipitate was filtered, and washed with benzene and ether. By evaporation of the filtrate, 13 g. of unaltered 2,4-dimethyl-5-thiazolylacetonitrile was recovered.

The precipitate was treated with 400 cc. of water, and 15.5 g. of colorless insoluble material removed. This material could be dissolved in hot dilute mineral acids, and crystallized when the solution was made ammoniacal. It was not studied further.

The clear alkaline filtrate of the insoluble material was acidified to *p*H 6.5, the precipitated cyano ketone was filtered, and washed with a little water. The almost colorless crystals weighed 34.5 g., and no appreciable additional amount could be obtained from the filtrate by evaporation at *p*H 6–7. Recrystallization from ethanol-water yielded colorless needles which sintered very slightly at 114°, and seemed to re-solidify at 120°. On heating to 200°, they darkened, and decomposed completely at 204–205°.

Anal. Calc'd for $C_9H_{10}N_2OS$: N, 14.42. Found: N, 14.44.

Hydrolysis of the cyano ketone with 15% sulfuric acid led to almost complete recovery of 2,4-dimethylthiazole-5-acetonitrile, and only very small amounts of an oily non-ketonic by-product were collected.

2-Benzyl-4-thiazolylacetic acid. The crude ethyl γ-bromoacetoacetate from 800 g. of ethyl acetoacetate was added to a well agitated ice-cold suspension of 300 g. of phenylthioacetamide in 1 liter of ethanol over a period of 90 minutes. When about one-half of the bromo ester had been added, the mass solidified but became more liquid and lumpy as the reaction proceeded. The mixture stood in ice for two hours, and at 25° for 48 hours; it liquefied during this latter period. The solvent was distilled under reduced pressure, the brown oily residue treated with 0.1 *N* hydrochloric acid, the aqueous solution was separated, washed with ether, and made alkaline with sodium carbonate. The oily ethyl 2-benzyl-4-thiazolylacetate was extracted into three portions of ether, the ether solution dried, filtered, and the solvent distilled. The crude ethyl ester (10 g.) was converted to the amide as described below.

The *picrate* of the ethyl ester crystallized from ethanol as yellow leaflets, melting at 109–110° after slight sintering.

Anal. Calc'd for $C_{20}H_{18}N_4O_9S$: N, 11.43. Found: N, 11.48.

The aqueous alkaline mother liquor of the ethyl ester was acidified slightly with acetic acid, and 2-benzyl-4-thiazolylacetic acid precipitated as colorless felted needles. It was recrystallized from dilute ethanol and melted at 126.5–128°. The yield was 31 g.

Anal. Calc'd for $C_{12}H_{11}NO_2S$: N, 6.01. Found: N, 5.87.

The acid was suspended in 200 cc. of ether and methylated with 0 5 g. of diazomethane. All but 0.5 g. of the acid went into solution in a rapid reaction. The ether solution was washed with sodium carbonate solution and water, dried, the solvent distilled, and the residual crude oily methyl 2-benzyl-4-thiazolylacetate converted to the amide.

In a second experiment, no free 2-benzyl-4-thiazolylacetic acid but only the ethyl ester was obtained. The yield was 81 g.

2-Benzyl-4-thiazolylacetamide. Nineteen grams of crude methyl (or ethyl) 2-benzyl-4-thiazolylacetate was shaken with 150 cc. of 20% ammonium hydroxide overnight, the solidified practically pure amide filtered, and washed with 50 cc. of water. The yield was 17 g. It was recrystallized from a little ethanol and appeared as colorless flat glittering leaflets, m.p. 132–133°.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: N, 12.06. Found: N, 12.01, 11.75

2-Benzyl-4-thiazolylacetonitrile. The amide was refluxed with a tenfold volume of phosphorus oxychloride for twenty minutes, and the mixture worked up as usual. The solid nitrile was fairly insoluble in dilute acids, but complete precipitation occurred after the acid solution had been made alkaline. It was purified by solution in ether, filtration from some insoluble by-product, and fractionation; the pale yellow oil boiled at 203–205° (3–4 mm.); the yield was 76%. Recrystallization from dilute ethanol with the aid of Darco furnished colorless needles, m.p. 43–44°.

Anal. Calc'd for $C_{12}H_{10}N_2S$: N, 13.07. Found: N, 12.97.

β-(2-Benzyl-4-thiazolyl)ethylamine. A solution of 14 g. of 2-benzyl-4-thiazolylacetonitrile in 200 cc. of saturated absolute ethanolic ammonia was hydrogenated with the aid of 7 g. of Raney nickel catalyst under atmospheric pressure. The reduction was complete within a few hours, and the mixture worked up in the customary manner. Fractionation of the oily amine yielded 7.5 g. of a colorless distillate, b.p. 162–165° (2 mm.) which attracted carbon dioxide from the air with the formation of a solid addition compound.

The *dipicrate* crystallized from ethanol as felted yellow needles, m.p. 143.5–144.5°.

Anal. Calc'd for $C_{12}H_{14}N_2S \cdot 2C_6H_2N_3O_7$: N, 16.56. Found: N, 16.47.

The base was recovered from the pure picrate and converted to the *dihydrochloride* in acetone-ether solution. After recrystallization from ethanol-ether, the colorless crystals melted at 167–170°.

Anal. Calc'd for $C_{12}H_{14}N_2S \cdot 2HCl$: N, 9.62. Found: N, 9.16, 9.36.

Thiobenzamide. The method of Gabriel and Heyman (14) was modified as follows. A solution of 200 g. of benzonitrile in 800 cc. of ethanol was saturated with ammonia in the cold, and then hydrogen sulfide was passed in at a moderate rate for 60 hours. The mixture was poured into 4 l. of water, the precipitated thioamide filtered, washed with water, and dried in the air. It melted at 108–111° without recrystallization. The yield was practically quantitative.

2-Phenyl-4-methyl-5-thiazolylacetic acid. A solution of 65 g. of thiobenzamide in 450 cc. of boiling absolute ethanol was treated with the crude ethyl β-bromolevulinate prepared from 100.8 g. of ethyl levulinate, over a period of ten minutes. Only a moderate exothermic reaction occurred, the solution first turning red and then again lighter. After refluxing for 24 hours, dilute hydrochloric acid was added, some insoluble hydrobromide filtered, the filtrate concentrated to remove excess ethanol, and extracted with ether. The ether solution was washed with dilute hydrochloric acid, and the combined acid solutions were allowed to stand. They deposited crystals of ethyl 2-phenyl-4-methyl-5-thiazolylacetate hydrobromide, which after combination with the insoluble precipitate previously filtered, weighed 43.5 g. The salt was recrystallized from ethanol-ether. The colorless crystals were sparingly soluble in water with partial hydrolysis and melted at 170–172° after sintering at 167°.

Anal. Calc'd for $C_{14}H_{15}NO_2S \cdot HBr$: N, 4.09. Found: N, 4.22.

When the acid mother liquors of the hydrobromide were neutralized with sodium carbonate, and buffered with a little acetic acid, 2 g. of ammonium 2-phenyl-4-methyl-5-thiazolylacetate precipitated. Two recrystallizations from absolute ethanol yielded fine colorless needles, m.p. 228–229°.

Anal. Calc'd for $C_{12}H_{14}N_2OS$: N, 11.91. Found: 11.71.

2-Phenyl-4-methyl-5-thiazolylacetamide. (a) The amide was prepared from ethyl 2-phenyl-4-methyl-5-thiazolylacetate hydrobromide according to the general directions given in a similar case by Price and Pickel (6). It was precipitated from the reaction mixture in a yield of 56% and was recrystallized from dioxane and finally from dilute ethanol. The colorless needles melted at 168–169°.

Anal. Calc'd for $C_{12}H_{12}N_2OS$: N, 12.06. Found: 12.00.

(b) One gram of ammonium 2-phenyl-4-methyl-5-thiazolylacetate was warmed gently with 10 cc. of thionyl chloride for a few minutes, and the red solution allowed to stand overnight. The excess thionyl chloride was distilled under reduced pressure, and 20 cc. of 20% ammonium hydroxide added to the cooled residue After a vigorous reaction the tarry residue solidified. The amide, obtained in almost quantitative yield, was washed with water and recrystallized once from dilute ethanol. It melted at 167–168°.

2-Phenyl-4-methyl-5-thiazolylacetonitrile. The amide just described was dehydrated with ten times its weight of phosphorus oxychloride, and the mixture worked up as in the analogous cases. The nitrile was very little soluble in dilute acids but was best extracted into ether from an alkaline solution. The ether extract had to be filtered from a small but voluminous tarry precipitate before being washed, and dried over sodium sulfate. The nitrile was purified by distillation; it boiled at 194–196° (6 mm) and solidified in the receiver. It was finally recrystallized from slightly dilute ethanol, the colorless needles melting at 104.5–106°. The yield was nearly quantitative.

Anal. Calc'd for $C_{12}H_{10}N_2S$: N, 13.07. Found: 13.07.

β-(2-Phenyl-4-methyl-5-thiazolyl)ethylamine. After several trials, the following conditions seemed to give the best results.

A solution of 6 g. of 2-phenyl-4-methyl-5-thiazolylacetonitrile in 400 cc. of absolute ethanol containing 8 g. of potassium hydroxide was hydrogenated with 10 g. of Raney nickel catalyst under ordinary pressure. About 75% of the calculated amount of hydrogen was absorbed in two days, the catalyst filtered, the solvent removed under reduced pressure, and the residue taken up in dilute hydrochloric acid. The acid solution was washed with ether to remove traces of unreduced nitrile, made alkaline, and the amine extracted with three portions of ether. The oily amine from the ether extract boiled at 155–170° (4 mm.).

The *dipicrate* crystallized from ethanol. After several recrystallizations from much ethanol the orange prisms sintered at 210°, blackened and decomposed at 220–230°, and melted at 238–239° with complete decomposition.

Anal. Calc'd for $C_{24}H_{20}N_8O_{14}S$: N, 16.57. Found: N, 17.05.

The base was regenerated from the picrate by means of lithium hydroxide solution, and converted to its *dihydrochloride* in ethanol-acetone. Recrystallization from the same solvent mixture furnished colorless crystals, m.p. 218–220°.

Anal. Calc'd for $C_{12}H_{14}N_2S \cdot 2HCl$: Cl, 24 35; N, 9.62.
Found: Cl, 23.93; N, 9.61.

2-Benzylthiazole. To a boiling solution of 50 g. of phenylthioacetamide in dry benzene, 47 g. of freshly distilled chloroacetaldehyde hydrate was added dropwise with shaking and heating. The reaction was not vigorous; the mixture separated into two layers, the lower one darkening soon. It was refluxed for two and one-half hours with occasional shaking, cooled, diluted with water, made strongly acidic, and the resulting thick emulsion broken up by filtration through Darco. The benzene layer was separated, the acid solution made alkaline with sodium hydroxide and extracted four times with ether. During the first extraction, another bad emulsion occurred which had to be removed as the one above. During the drying of the combined ether extracts with potassium hydroxide, a brown flocculent tar appeared which was filtered before distilling off the ether. The remaining dark oil was fractionated. A colorless oil weighing 35 g. (60.4%) distilled at 106–107° (3 mm.) or 104° (2 mm.) and showed n_D^{20} 1.5919. It was not readily soluble in one equivalent of acid, and darkened on standing.

The *picrate* crystallized from ethanol as yellow needles, m.p. 162–162.5° (decomp.), after some sintering at 157.5°.

Anal. Calc'd for $C_{16}H_{12}N_4O_7S$: N, 13.86. Found: N, 13.99.

2-Benzylthiazoline. A mixture of 3.5 g. of β-bromoethylammonium bromide and 2.5 g. of phenylthioacetamide was heated to 130°; it melted with slight darkening and evolution of gas. The temperature was raised to 190–200° for one hour, the mass was cooled, dissolved in 20 cc. of water, the solution cleared with Darco, made alkaline and extracted twice with ether. The ether extract was washed with water, dried over potassium hydroxide, and the oily residue from this extract distilled. It weighed 1.3 g. and boiled at 125–126° (3–4 mm.) or 135–136° (7 mm.). The colorless oil turned dark on standing.

The *picrate* crystallized from ethanol as long yellow needles, m.p. 141–142°. It was readily soluble in water.

Anal. Calc'd for $C_{16}H_{14}N_4O_7S$: N, 13.83. Found: N, 14.04.

SUMMARY

A number of β-pyridylisopropylamine derivatives, and β-thiazolylethylamines have been prepared. The amines in the pyridine series were obtained by converting α-picoline and some of its derivatives to the corresponding α-pyridyl acetones, and subjecting the ketones to the Leuckart reaction. The thiazolylethylamines were formed by condensing bromo keto esters with thioamides, and converting the resulting alkyl thiazolyl acetates through the amides and nitriles to the amines. Syntheses leading toward β-(4-thiazolyl)ethylamine, and the preparation of two thiazolyl α-cyano ketones are reported.

Several of the primary amines showed analgesic activity. A hypothesis distinguishing them from similar compounds which exhibit histamine-type effects has been advanced.

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[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL WORKS]

ISOLATION AND PURIFICATION OF NEOPINE

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The only record of the isolation of the rare opium alkaloid neopine is a sample from T. & H. Smith and Co., Edinburgh, used by Dobbie and Lauder (1) and Van Duin, Robinson, and Smith (2) in determining its structure, and one prepared by A. C. Boylston of this company used by D. E. Jackson (3) in studying its pharmacological action. The methods used for its separation and purification by earlier investigators have not been published. It seems appropriate therefore to describe the procedures we have employed to isolate neopine and to record our observations on its properties.

Neopine was first observed during attempts to evaluate tarry mother liquors from the isolation of codeine from opium. Its hydrobromide was much more soluble than codeine hydrobromide and its sulfate failed to crystallize. After purification, its physical properties agreed closely with the reports of previous workers, and its reduction to dihydrocodeine was confirmed.

Neopine sulfate was prepared and found to differ markedly from codeine sulfate. It did not crystallize from water and indeed seemed to be unstable in the presence of moisture. It was much more soluble in alcohol than was codeine sulfate, and this property makes possible the relatively easy separation of these alkaloids.

Since neopine differs structurally from codeine only in the position of the double bond, it seemed possible to us that it might be formed by isomerization of codeine during crystallization operations. Accordingly a search for neopine was made in the mother liquors of codeine prepared from morphine. No evidence for the presence of neopine was found and it was concluded that neopine occurs as such in opium.

We wish to express our appreciation to Dr. Lyndon Small for his interest and encouragement.

EXPERIMENTAL

Isolation. The starting material for isolation of neopine was the last mother liquor from crystallization of crude natural codeine sulfate or hydrobromide from Turkish opium. A typical procedure was as follows:

Twenty-seven liters of concentrated black tarry hydrobromide mother liquor from which no more crystals separated after three months storage was diluted with 76 l. of boiling water in which 500 g. of sodium chloride had been dissolved. The solution was filtered with the aid of diatomaceous earth, and the filtrate was extracted three times with 23-l. portions of chloroform to remove tars, which were discarded. The aqueous phase was stirred with 38 l. of benzene and made alkaline to phenolphthalein by addition of 10 *N* sodium hydroxide solution. The benzene layer was separated and extraction was repeated three times more with 38-l. portions of benzene. The solvent was removed from the combined extracts by distillation; the residue, still containing some solvent, amounted to 5.4 kg. of a thick brown syrup. This was dissolved in 14.l. of acetone and acidified to Congo Red by adding 3.5 l. of 40% aqueous hydrobromic acid. The crude neopine hydrobromide separated in crystalline form. It was centrifuged, washed with acetone and dried at 100°. The product was a light tan powder weighing 2.2 kg. Its specific rotation in water was $[\alpha]_D^{30}$ +14° (*c*, 3.738).

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Neopine hydrobromide. The crude hydrobromide was purified by dissolving one part by weight in four parts of boiling water, decolorizing the solution with activated carbon (Darco G60) and cooling to 2°. The first crop of crystals amounted to a 60% recovery. Three or four recrystallizations gave a colorless product. When heated in a capillary tube in a Berl and Kullmann block it turned pink at 235°, darkened at 240° and decomposed at 280–285°. The specific rotation in water was $[\alpha]_D^{27}$ +16.99° (*c*, 3.806). Dobbie and Lauder reported darkening at 240° and decomposition at 282–283°, $[\alpha]_D^{20}$ +17.07° (*c*, 5.188), +17.4° (*c*, 5.074); Van Duin and co-workers gave $[\alpha]_D^{23}$ +17.32° (*c*, 3.696).

Neopine hydrobromide is about 7 times as soluble in cold water as codeine hydrobromide. Recrystallization from water of a mixture containing about 85% neopine hydrobromide results in little change in the proportions. If the per cent of neopine hydrobromide is less than 85%, it will concentrate in the mother liquors, while if greater, pure neopine hydrobromide may be obtained by several recrystallizations.

Neopine alkaloid. A water solution of the hydrobromide, 10 g. in 100 cc. of warm water, was made alkaline with potassium carbonate and extracted 5 times with equal volumes of ether. Evaporation of the solvent left a syrup which crystallized on standing, or more rapidly if seeded. The alkaloid was purified by dissolving 6.5 g. in 100 ml. of boiling cyclohexane, decolorizing with activated carbon (Darco G60) and cooling to 20°, which gave an 80% recovery of the base in the form of long needles. Cooling the cyclohexane solution below 20° gave a thick opalescent gel which remelted on warming. A similar gel formed with methylcyclohexane. The alkaloid was recrystallized also from hexane (Skellysolve B, b.p 60–70°) containing 2.5% by volume of ethanol; it is soluble to the extent of about 2 g. per 100 ml. of the boiling solution and separates on slow cooling as long glistening needles in 75% yield. Neopine is not sufficiently soluble in ether or petroleum ether for convenient recrystallization of large amounts.

Neopine alkaloid melted at 127.5–127.8° (corr.) and its specific rotation in chloroform was $[\alpha]_D^{26}$ −28.13° (*c*, 7.767); −30.50° (*c*, 3.904). Van Duin and co-workers reported m.p. 127–127.5° (corr) and $[\alpha]_D^{26}$ −28.10° (*c*, 7.4740).

Neopine sulfate. A solution of 4 g. of neopine in 400 ml. of acetone was acidified by adding a solution of sulfuric acid in anhydrous acetone (0.65 g. per 100 ml.) until a test drop reacted acid to litmus but alkaline to chlorophenol red. Neopine sulfate separated rapidly as very fine crystals, was collected with minimum exposure to moisture, and dried at 60°. When heated in a sealed capillary it softened at 163–165° and melted with frothing at 166–167°. Its rotation in water was $[\alpha]_D^{28}$ +16.38° (*c*, 3.000). The salt was soluble in 65–70 parts of 99% alcohol, 4–5 parts of 95% alcohol and 2.5–3 parts of 80% alcohol. It was very soluble in water, giving a solution which was neutral to methyl red. However, after four months in a stoppered flask, the solution had become somewhat brown and its specific rotation had increased 2°. When the dry salt was exposed to the atmosphere it turned brown and caked, but when sealed in an ampoule it remained white and powdery.

Reduction of neopine. Five g. of neopine hydrobromide dissolved in 100 ml. of water was shaken with 0.2 g. of platinum oxide catalyst (Baker and Co.) and hydrogen at atmospheric pressure. The reduction came to a stop after 50 minutes, when 375 ml. of hydrogen had been absorbed. After filtering off the catalyst, the solution was made alkaline with sodium hydroxide and extracted four times with 50 ml. of chloroform. The syrup remaining after evaporation of the solvent was recrystallized from 25 ml. of petroleum ether (b.p 30–60°) containing 5 ml. of benzene. The crystals of dihydrocodeine which formed melted at 112–113°, which is in agreement with the literature (4). The mother liquor from the recrystallization was evaporated; the syrupy residue was taken up in 20 ml. of hot alcohol and mixed with a solution of 5 g. of tartaric acid in 20 ml. of hot alcohol. On cooling and stirring dihydrocodeine acid tartrate crystallized; it melted at 187–189°, which is in agreement with previous reports.

Separation of codeine and neopine mixtures. A method was developed of separating mixtures of codeine and neopine based on the difference in solubility of the sulfates in 95% alcohol. One part of codeine sulfate dissolves in about 1000 parts of 95% alcohol, while one part of neopine sulfate dissolves in 4 or 5 parts. The procedure may be illustrated by the following typical example: Ten g. of a 1-to-1 mixture of codeine and neopine alkaloids was dissolved in 75 ml. of dry acetone and a solution of 2 g. of sulfuric acid in 150 ml. of dry acetone was added until the solution reacted neutral to bromophenol blue. The mixed sulfates crystallized out immediately; the solution was chilled and filtered and the salt was air-dried. The dry salts were triturated two times with 100-ml. portions of 95% alcohol; the supernatant solution was decanted each time through a filter. The insoluble crystalline codeine sulfate remaining was dissolved in water, precipitated with potassium carbonate and extracted with several portions of chloroform. The dried chloroform extracts were evaporated and the residue converted to the hydrobromide from acetone. The rotation of the codeine hydrobromide was $[\alpha]_D^{28}$ $-91°$ (c, 2.0, water) compared to $-96.6°$ given by Martin (5).

The combined alcoholic extracts of the mixed sulfates were evaporated to small volume, taken up in water, and the alkaloid extracted and converted to the hydrobromide as before. The rotation of this hydrobromide was $[\alpha]_D^{28}$ $+4.5°$ (c, 3.7, water). Assuming a straight line relationship between specific rotation and per cent composition for mixtures of codeine and neopine hydrobromides it was estimated that the material remaining undissolved from the alcoholic trituration and giving a hydrobromide with a specific rotation of $-91°$ was 96% codeine. The specific rotation of $+4.5°$ corresponds to 89% neopine in the material dissolved in the alcoholic extracts. From such material pure neopine can be prepared by the procedure described.

SUMMARY

Neopine has been isolated from the mother liquors after crystallization of codeine. Neopine sulfate has been prepared and found to afford a means of separating neopine from codeine. No neopine was found in the mother liquors of codeine prepared from morphine.

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

SOME REACTIONS OF NEOPINE

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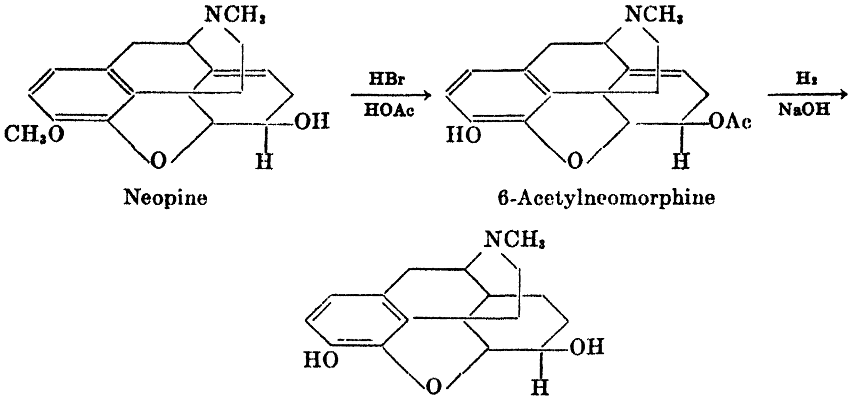
The rare opium alkaloid neopine was first described in the form of salts and methiodide by Dobbie and Lauder (1), who believed it to be a hydroxycodeine through misinterpretation of their analytical results; they presented no evidence for two hydroxyl groups. The base was obtained crystalline by van Duin, Robinson, and Smith (2), who demonstrated that it was an isomer of codeine, differing from this alkaloid only in the position of the hydroaromatic unsaturation.

Through the courtesy of Dr. V. H. Wallingford and Dr. A. H. Homeyer, of the Mallinckrodt Chemical Works, a quantity of highly purified neopine hydrobromide has been supplied for investigation, and I present herewith some of the reactions of this neglected alkaloid. In confirmation of Robinson's work, analysis shows the formula to be $C_{18}H_{21}NO_3$. Although there is not the slightest reason to doubt the results of the English investigators, the important transformation of neopine methohydroxide to β-methylmorphimethine in a single step has been verified. The low rotatory power of neopine derivatives (mostly around ±20°) and the extraordinary effect of opening the nitrogen-containing ring (+414°) are of theoretical interest.

In contrast to codeine, neopine can be demethylated in excellent yield with hydrogen bromide in glacial acetic acid; at the same time, acetylation of the 6-hydroxyl group takes place, as observed by Mosettig (3) in the parallel demethylation of dihydro-β-methylmorphimethine, so that the product is 6-acetylneomorphine, a strongly phenolic, sparingly water-soluble base. It is probable that the primary demethylation product is diacetylneomorphine, which undergoes half-hydrolysis during isolation, for if the diacetylneomorphine described below is dissolved in dilute acetic acid and recovered by a parallel procedure, it is regained as the monoacetyl derivative. The demethylation can also be accomplished with 48% aqueous hydrobromic acid but the product (neomorphine) is difficult to isolate in good yield because of its water-solubility.

By hydrogenation, 6-acetylneomorphine is converted to 6-acetyldihydromorphine, identical with the compound obtained by half-hydrolysis of diacetyldihydromorphine with hydroxylamine hydrochloride. The 6-acetyldihydromorphine *ex* neopine can be hydrolyzed easily to dihydromorphine. This confirms in a slightly different way the relationship established by Robinson between neopine and dihydrocodeine.

6-Acetylneomorphine is hydrolyzed readily by hot dilute alkali, yielding neomorphine, whose unexpected water-solubility causes some difficulty in the separation from inorganic material. Neomorphine crystallizes best from chloroform, in coffin-shaped prisms containing one molecule of chloroform. That no change in structure took place in the demethylation reaction is shown by the above-mentioned hydrogenation of 6-acetylneomorphine, and by the transformation of neomorphine·$CHCl_3$ back to neopine in quantitative yield by the action of diazomethane.



Neopine 6-Acetylneomorphine

Dihydromorphine

6-Acetylneomorphine, with acetic anhydride in pyridine, yields diacetylneomorphine, the analog of heroin. Other reactions of neopine and neomorphine will be discussed in a later publication.

The analgesic action of neopine, neomorphine, 6-acetylneomorphine, and diacetylneomorphine has been studied by Dr. N. B. Eddy, using the Woolfe-Macdonald (4) technique. The analgesic effectiveness of all four compounds is definitely less than that of their morphine analogs, the latter being 2 to 6 times more effective. There is not a consistent difference in toxicity; neopine and neomorphine are about one-half as toxic as codeine and morphine respectively, while 6-acetyl- and diacetyl-neomorphine are more toxic than their morphine analogs. It is remarkable that with all four compounds the Straub reaction is entirely absent, and in the main, convulsant action is less marked.

I am indebted to C. A. Kinser and Betty Mount of this Laboratory for the microanalyses.

EXPERIMENTAL

Neopine. The material used in this investigation was in part alkaloid of m.p. 127.5–128.5°, $(\alpha)_D^{28} -28.13°$, and in part hydrobromide of $(\alpha)_D^{27} +16.99°$, as described by Homeyer and Schilling (5). The composition of the alkaloid was verified.

Anal Calc'd for $C_{18}H_{21}NO_3$: C, 72.2; H, 7.23.

Found: C, 72.4; H, 7.30.

Neopine hydrochloride shows $(\alpha)_D^{20} +18.2°$ (water, *c*, 1.04). Neopine methiodide has $(\alpha)_D^{20} +23.5°$ (alcohol, *c*, 0.62).

Degradation to β-methylmorphimethine. Boiling neopine methiodide with 30% KOH for 10 min. resulted largely in unchanged methiodide. One gram of neopine in 10 ml. of benzene was treated dropwise with dimethyl sulfate. In contrast to Robinson's description, the methomethyl sulfate crystallized immediately in sparkling white flakes. The isolated salt was, however, too hygroscopic for further characterization. It was added immediately to 10 ml of 30% KOH and boiled gently for 3 min., when separation of pale yellow granular crystals was complete. These were filtered on a glass-wool mat and washed well with water; 0.95 g., m.p. 131–133°. It was recrystallized from ethyl acetate and from alcohol, 0.6 g., m.p. 136°, $(\alpha)^{20}_{D}$ +414° (95% alcohol, *c*, 1.03).

For purest β-methylmorphimethine *ex* codeine, m.p. 136°, $(\alpha)^{20}_{D}$ +413° (95% alcohol, *c*, 1.02). Knorr (6) reported m.p. 134–135°, $(\alpha)^{17}_{D}$ +438° in 97% alcohol.

Equal amounts of the "neopinemethine" and authentic β-methylmorphimethine were mixed and recrystallized from alcohol; m.p. 136°.

Demethylation of neopine: 6-acetylneomorphine. A suspension of 10 g. of neopine hydrobromide in 60 ml. of 15% hydrogen bromide in gl. acetic acid was heated slowly in the oil-bath. At 115° (bath-t.) vigorous evolution of gas began. The bath was raised to 145° in the course of an hour. The cooled, colorless solution was diluted with an equal volume of water and made alkaline with ammonia, scratching or seeding near the neutral point.

After 2 hrs. at 0°, the crystalline product was washed with a small amount of ice-water (fairly soluble); faintly pink crystals, 7.6 g. (88%).

From 73 ml. of alcohol, 5.1 g. (59%) was obtained; m.p. 243–251° (evac. tube, decomp.), $(\alpha)^{20}_{D}$ +27.6° (alcohol, *c*, 1.07).

Anal. Calc'd for $C_{19}H_{21}NO_4 + 1.5\ H_2O$: C, 64.4; H, 6.78.
Found: C, 64.5, 64.3; H, 6.66, 6.47.

The hydrate water could not be determined directly because of slight sublimation.

The hydrochloride was prepared with alcoholic HCl, and purified from absolute alcohol; it is extremely soluble in water. It had the m.p. 238–245° (evac. tube, decomp.), $(\alpha)^{20}_{D}$ +8.8° (water, *c*, 1.02).

Anal. Calc'd for $C_{19}H_{22}ClNO_4$: C, 62.7; H, 6.09.
Found: C, 62.9; H, 6.46.

Diacetylneomorphine. Five grams of 6-acetylneomorphine in 20 ml. of pyridine and 10 ml. of acetic anhydride was allowed to stand 24 hours. Liquid was removed as far as possible under diminished pressure, then over sulfuric acid in a high vacuum. Sat'd NaCl solution and sodium bicarbonate were added, and the emulsion extracted with ether. This left a syrup, which slowly crystallized, 5.6 g. It was very soluble in most media, quite soluble in hot water, 1% in cold water, but crystallized poorly. It was purified from ligroin (90–100°), 3.2 g., m.p. 127–127.5°, mixed m.p. with neopine 98–102°. In 95% alcohol it showed $(\alpha)^{20}_{D}$ +17.5° (*c*, 1.08).

Anal. Calc'd for $C_{21}H_{23}NO_5$: C, 68.3; H, 6.28.
Found: C, 68.4; H, 6.46.

Neomorphine. Ten grams of 6-acetylneomorphine was boiled for 10 min. with 40 ml. of 2 *N* NaOH. The solution was saturated with CO_2 (remained clear and colorless), and taken to dryness in the vacuum desiccator; it was necessary to break up frequently a tough surface skin. The dry powder was digested thoroughly with two 100-ml. portions of chloroform (filtering through "Supercel"). The acidified residue gave only a faint Mayer's test. The chloroform was distilled to about 30 ml., where crystals separated, 9 g., m.p. 103° (frothing). It was purified from chloroform, 5 g., m.p. 107° (±2°, the m.p. is difficult to determine accurately, as the froth is as white as the crystals). The crystals have a very characteristic "coffin shape"; in U.S.P. chloroform $(\alpha)^{20}_{D}$ −18.2° (*c*, 1.04), in 95% alcohol $(\alpha)^{20}_{D}$ −9.2° (*c*, 1.09).

Anal. Calc'd for $C_{17}H_{19}NO_3 + CHCl_3$: $CHCl_3$, 29.5.
Found: loss in wght., 100°/0.1 mm.: 29.5.
Calc'd for $C_{17}H_{19}NO_3$: C, 71.6; H, 6.71.
Found: C, 71.5; H, 6.85.

The solvent-free base has the m.p. 240–241° (evac. tube, decomp.). Both the dried and solvated product were readily soluble in water; ferric chloride test blue-green, Marquis' reagent red-violet, indistinguishable from that of morphine.

The *hydrochloride* was prepared with alcoholic HCl and purified from 95% alcohol containing HCl, granular, glassy crystals, m.p. 295–298° (evac. tube, decomp.); in water $(\alpha)^{20}_{D}$ +22.6° (*c*, 1.02).

Anal. Calc'd for $C_{17}H_{20}ClNO_3$: Cl, 11.0. Found: Cl, 10.5.

The salt tends to lose hydrogen chloride, and after two crystallizations from alcohol had the approximate composition $B_2 \cdot HCl$ (calc'd: C, 67.2; H, 6.66. Found: C, 68.2; H, 6.54); $(\alpha)^{20}_{D}$ +19.7° (water, *c*, 1.06).

Conversion of 6-acetylneomorphine to dihydromorphine. 6-Acetylneomorphine in 0.2 *N* HCl with platinum oxide absorbed the calculated amount of hydrogen in 40 min. Treatment with sodium carbonate precipitated the base crystalline; from alcohol, glassy needles of *6-acetyldihydromorphine*, m.p. 245° (evac. tube); $(\alpha)^{20}_{D}$ −117° (95% alcohol, *c*, 1.04). Authentic 6-acetyldihydromorphine, obtained by half-hydrolysis of diacetyldihydromorphine with warm aqueous hydroxylamine hydrochloride, had the m.p. 246° (evac. tube), $(\alpha)^{20}_{D}$ −117° (95% alcohol, *c*, 1.04). Both specimens were instantly soluble in dil. NaOH; ferric chloride reaction deep pure blue. 6-Acetyldihydromorphine hydrochloride has $(\alpha)^{20}_{D}$ −110.5° (water, *c*, 1.78).

Anal. Calc'd for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.04.
Found (base *ex* neopine): C, 69.2; H, 7.18.

Brief treatment of either product with hot 3 *N* NaOH gave dihydromorphine hydrate, purified from alcohol; both specimens, slow heating (2°/min.), gave an opaque melt at 135°, resolidifying and melting at 207°. With rapid heating the literature m.p. 155–157° (7) was observed. These melting point phenomena of dihydromorphine were first described by D. E. Morris (8).

SUMMARY

The degradation of neopine to β-methylmorphimethine in a single step has been verified. Neopine can be demethylated smoothly to 6-acetylneomorphine, which yields on acetylation diacetylneomorphine, or on deacetylation, neomorphine, a new isomer of morphine. By hydrogenation of 6-acetylneomorphine, followed by hydrolysis, dihydromorphine is obtained; this confirms the nature of the isomerism.

BETHESDA 14, MD.

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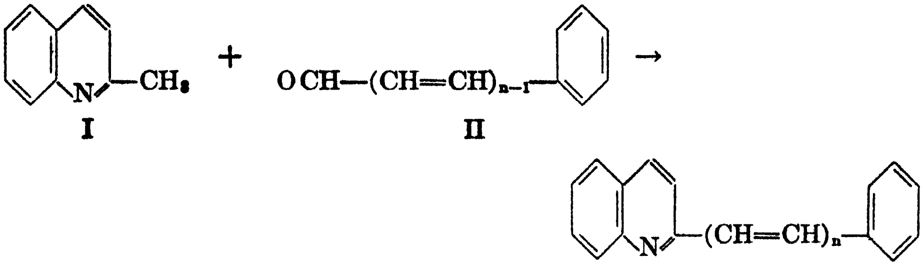
[Contribution from the Sterling Chemistry Laboratory, Yale University]

THE PREPARATION AND ABSORPTION SPECTRA OF α-(α-QUINOLYL)-ω-PHENYLPOLYENES[1]

CHARLES COMPTON[2] AND WERNER BERGMANN

Received June 10, 1946

The classical studies by Kuhn and Winterstein (1) on the synthesis and the chemical and the physical properties of diphenylpolyenes have not only materially assisted in the elucidation of the structure of carotenoids, but have also provided significant examples illustrating the relations which exist between the color and constitution of organic compounds. The present paper deals with an extension of such studies to a series of heterocyclic polyenes which differ from the diphenylpolyenes solely in the replacement of one terminal phenyl group by the α-quinolyl group. The first two members of this series (III, n = 1, 2) have been known for some time. Their preparation was first accomplished by Wallach (2) and Renz (3) through the condensation of quinaldine (I) with benzaldehyde (II, n = 1) or cinnamaldehyde (II, n = 2).



III. α-(α-Quinolyl)-ω-phenylpolyene

This general method has more recently been modified by Pfeiffer (4) and Spaeth (5). The phenylpolyenals necessary for an extension of this series have recently become more readily available through the elegant method described by Schmitt (6). Their condensation with quinaldine was carried out by heating the reagents with zinc chloride to about 100°, a procedure which combines certain features of the methods of Renz (3) and Spaeth (5). With the higher aldehydes, a large excess of quinaldine was required to dissolve the phenylpolyenal. For a direct comparison of the heterocyclic polyenes with the diphenylpolyenes, the latter were prepared according to the method of Kuhn and Winterstein (1).

As shown in Table I the colors of the quinolylphenylpolyenes present the same gradation as those of the diphenylpolyenes. In the heterocyclic series the first colored compound is the butadiene and its color shows a striking similarity to that of the diphenylhexatriene, the first colored compound of the diphenylpolyene series. The similarity of color between $C_9H_6N—(CH{=}CH)_n—C_6H_5$ and $C_6H_5—(CH{=}CH)_{n+1}—C_6H_5$ is even more pronounced among the higher vinylogs of the two respective series. On the basis of visual evidence it appears therefore, that the chromophoric character of the α-quinolyl group is equivalent to that of a styryl group.

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[1] The material in this paper constitutes part of a dissertation submitted by C. Compton in partial fulfillment of the requirements for the Ph.D. degree, Yale University, 1943.

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TABLE I

Comparison of Diphenyl- and α-Quinolyl-ω-phenyl-polyenes

n	$C_6H_5—(CH{=}CH)_n—C_6H_5$		$C_9H_6N—(CH{=}CH)_n—C_6H_5$	
	m.p. °C.	color	m.p. °C.	color
1	124	Colorless	98	Colorless
2	153	Colorless	117	Greenish-yellow
3	200	Greenish-yellow	160	Golden-yellow
4	232	Golden-yellow	195	Orange
5	253	Orange	—	—
6	267	Brown-orange	232	Copper-bronze
7	279	Copper-bronze	—	—

TABLE II

Absorption Maxima in Chloroform at 25°C

	λ max (mμ)		
	(a)	(b)*	(c)
Diphenylethylene	296	310	—
Diphenylbutadiene	319	333	350
Diphenylhexatriene	340	355	374
Diphenyloctatetraene	360	377	403
Diphenyldecapentaene	380	400	425
Diphenyldodecahexaene	396	420	444
Diphenyltetradecaheptaene	413	437	463
Quinolylphenylethylene	281	320	—
Quinolylphenylbutadiene	296	358	—
Quinolylphenylhexatriene	312	377	—
Quinolylphenyloctatetraene	—	398	—
Quinolylphenyldodecahexaene	—	435	457

* The (b) maximum is the most intense in each case except for diphenylethylene and phenylquinolylethylene in which cases the (a) maximum is the most intense.

This is also borne out by a comparison of the absorption spectra of the members of the two series, which were measured in a chloroform solution at 25°. Table II records the wave lengths of the absorption maxima of both series, and Figure 1 shows the spectra of the members of the heterocyclic series. These spectra, like those of the diphenyl series, show the typical increase of absorption intensity and curve character with the lengthening of the exocyclic chain.

Table III presents a comparison of the highest maxima of the various members of the heterocyclic- and diphenyl-polyene series. With the exception of the first member, the maximum of $C_9H_6N—(CH{=}CH)_n—C_6H_5$ lies practically at the same wave length as that of $C_6H_5—(CH{=}CH)_{n+1}—C_6H_5$. This relationship is also illustrated by Figure 2 which shows the striking similarity between the absorption spectra of 1-(α-quinolyl)-12-phenyldodecahexaene-1,3,5,7,9,11 and 1,14-diphenyltetradecaheptaene-1,3,5,7,9,11,13.

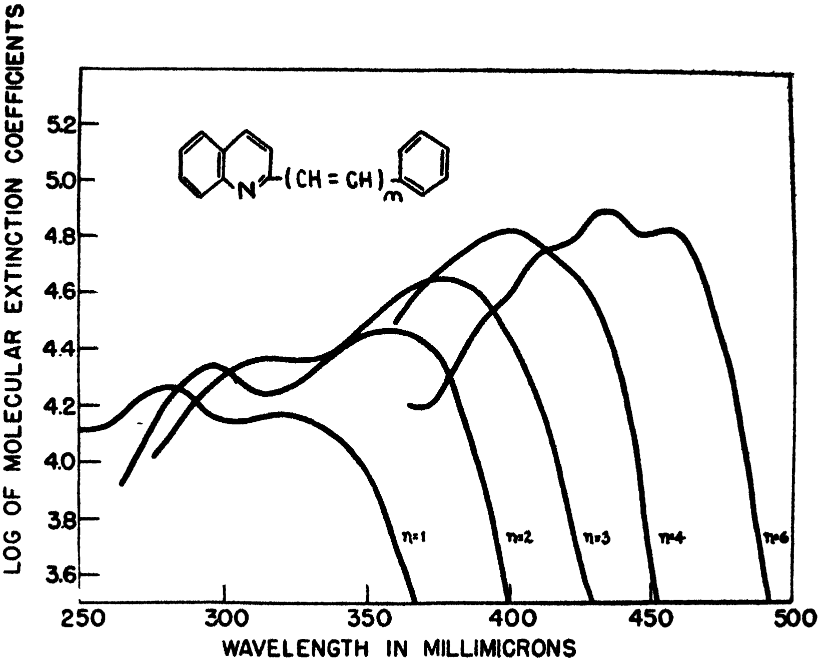

FIG. 1. Absorption curves of α-(α-quinolyl)-ω-phenylpolyenes in chloroform at 25°C.

TABLE III

COMPARISON OF ABSORPTION MAXIMA OF QUINOLYLPHENYL- AND DIPHENYL-POLYENES

max. (mμ) of $C_9H_6N—(CH{=}CH)_n—C_6H_5$				
n = 1	2	3	4	6
320	358	377	398	435
333	355	377	400	437
n = 2	3	4	5	7
max. (mμ) of $C_6H_5—(CH{=}CH)_n—C_6H_5$				

On the basis of the electronic oscillation concept, Lewis and Calvin (7) have formulated the equation $\lambda^2 = kn$, which relates λ, the wave length of the absorption maximum, to n, the number of double bonds in the exocyclic chain. The data for the diphenylpolyene series, particularly those of the higher members, are in excellent agreement with this relationship. As shown by Figure 3, the same relationship also exists in the α-(α-quinolyl)-ω-phenylpolyene series.

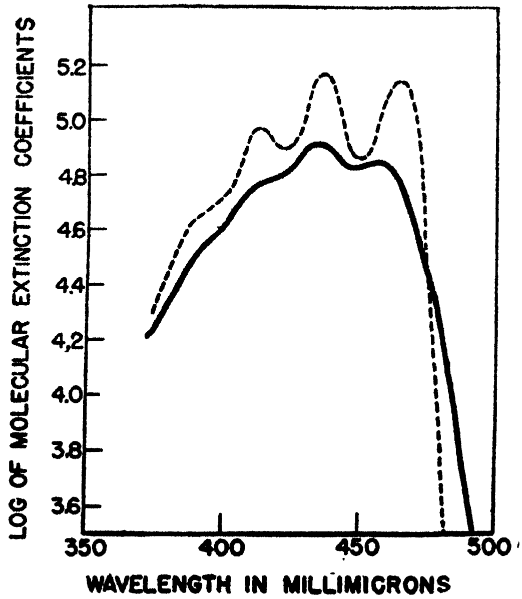

FIG. 2. Absorption spectra of 1-(α-quinolyl)-12-phenyldodecahexaene (solid line) and 1,14-diphenyltetradecaheptaene (broken line) in chloroform at 25°C.

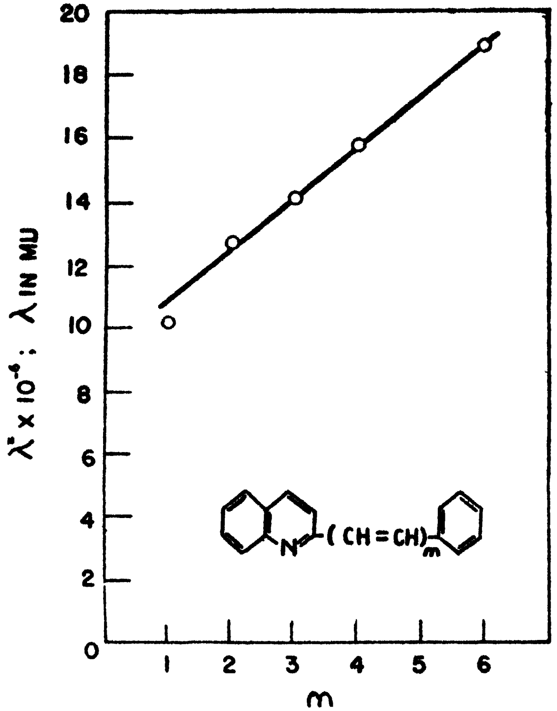

FIG. 3. Plot of the square of the wave length against the number of exocyclic double bonds.

EXPERIMENTAL

All melting points are corrected.

1-(α-Quinolyl)-2-phenylethylene(III, n = 1). This compound was prepared by the procedure of Pfeiffer *et al.* (4) with minor modifications. It melted at 98.4–98.6° (recorded m.p. 96°).

1-(α-Quinolyl)-4-phenylbutadiene-1,3 (III, n = 2). Method A. A mixture of 30 g. (0.23 mole) of freshly distilled cinnamaldehyde, 25 g. (0.18 mole) of freshly distilled quinaldine, and 3 g. of zinc chloride in a 200-cc. flask equipped with a reflux condenser was heated in an oil-bath to 115° for six hours. After cooling, 75 cc. of ethanol was added to the mixture, and the crystals which separated upon standing were washed with cold ethanol. Five recrystallizations from ethanol, including two treatments with Norit, gave 6.3 g. (13.5%) of the pure diene in form of shiny, greenish-yellow plates of m.p. 116.8–117.4° (recorded m.p. 117°).

Method B. A mixture of 6.6 g. (0.045 mole) of freshly distilled cinnamaldehyde, 7.2 g. (0.05 mole) of freshly distilled quinaldine, 2 g. of piperidine acetate and 35 cc. of 70% ethanol was kept at room temperature for forty days. The semicrystalline, dark-colored precipitate which had formed was filtered and dissolved in 35 cc. of ethanol. Upon cooling of the solution a yellowish, crystalline precipitate was slowly formed. After three recrystallizations from ethanol, including two treatments with Norit, 0.75 g. (6%) of a greenish-yellow material of m.p. 117.2–117.4° was obtained.

1-(α-Quinolyl)-6-phenylhexatriene-1,3,5 (III, n = 3). This compound was prepared from 5-phenylpentadienal (8) and quinoline by a method analogous to A, described above, except that the heating was carried out at 100°. The purest product which was obtained in a yield of 10.5% melted at 160.2–160.6° and crystallized from ethanol in form of golden-yellow plates. It is soluble in ethanol (1 part in 60 cc.), ether, benzene, and chloroform.

Anal. Calc'd for $C_{21}H_{17}N$: C, 89.01; H, 6.04.
Found: C, 88.84; H, 6.08.

1-(α-Quinolyl)-8-phenyloctatetraene-1,3,5,7 (III, n = 4). A mixture of 1.1 g. (0.006 mole) of 7-phenylheptatrienal (6) and 1.8 g. (0.012 mole) of freshly distilled quinaldine was heated gently in a test tube fitted with a stopper containing a capillary until the solid aldehyde had dissolved. About 0.2 g. of zinc chloride was added to the mixture which was then heated in an oil-bath for 70 minutes at 110°. The solid material was filtered, washed with cold ethanol and dried. It consisted of 0.6 g. of orange colored plates. The polyene was recrystallized three times from toluene, including two treatments with Norit, and finally from ethanol by continuous extraction through a thimble. The pure product, which was obtained in a yield of 10.7%, formed orange plates and melted at 194.8–195.6°. It is only slightly soluble in hot ethanol, and soluble in benzene, ether and chloroform.

Anal. Calc'd for $C_{23}H_{19}N$: C, 89.28; H, 6.19.
Found: C, 89.28; H, 6.17.

1-(α-Quinolyl)-12-phenyldodecahexaene-1,3,5,7,9,11 (III, n = 6). A mixture of 2 g. (0.0085 mole) of 11-phenylundecapentaenal (6), 15 g. (0.1 mole) of freshly distilled quinaldine, and 0.3 g. of zinc chloride was heated as described above for twenty-five hours at 97°. The dark red precipitate which had formed was filtered, washed with ethanol, and extracted from a thimble with hot toluene, an operation which took several days. Concentration of the extract gave a reddish, crystalline precipitate, which was washed with toluene, and once more recrystallized from this solvent. The final product, yield 4%, consisted of small, coppery-red plates, and melted at 232.4–232.8°. It is practically insoluble in ethanol, sparingly soluble in hot benzene and toluene, and soluble in chloroform to the extent of 3 mg. in 200 cc.

Anal. Calc'd for $C_{27}H_{23}N$: C, 89.71; H, 6.41.
Found: C, 89.24; H, 6.37.

ACKNOWLEDGMENT

The authors wish to express their gratitude to Mr. D. Richardson of the American Cyanamid Company for certain spectra measurements.

SUMMARY

A series of α-(α-quinolyl)-ω-phenylpolyenes has been prepared, and their absorption spectra have been measured and compared with those of the diphenylpolyene series.

It has been demonstrated that in the heterocyclic polyene series the chromophoric character of the α-quinolyl group is equivalent to that of a styryl group.

It has been shown that the relation $\lambda^2 = kn$ holds true in the α-(α-quinolyl)-ω-phenylpolyene series.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

1,6- (OR 2,5-) DISUBSTITUTED NAPHTHALENES[1]

CHARLES D. HURD, OTIS E. FANCHER, AND WILLIAM A. BONNER

Received September 16, 1946

The present study concerns itself with various new approaches to the problem of attaching substituents at the 1,6 positions of naphthalene, since several compounds of this type were desired for antimalarial investigations. One such approach was the Gattermann reaction with 2-chloronaphthalene, hydrogen cyanide, and aluminum chloride. An aldehyde was obtained, m.p. 100–102°, which changed to 7-chloro-1-naphthoic acid on oxidation. It was, therefore, the previously undescribed 7-chloro-1-naphthaldehyde. The fact that the crude aldehyde melted at 82–85° suggests that 6-chloro-1-naphthaldehyde (m.p. 83–84°) was also present.

Several new compounds were made from Cleve's acid, 5-amino-2-naphthalenesulfonic acid. These included sodium 5-cyano-2-naphthalenesulfonate made by the Sandmeyer reaction, 5-cyano-2-naphthalenesulfonyl chloride, and the corresponding anilide. Interchange of the SO_2Cl group by Cl was attempted by heating with phosphorus pentachloride at 160°, since there is precedent for this type of decomposition (1). In addition to the anticipated conversion of 5-cyano-2-naphthalenesulfonyl chloride into 6-chloro-1-naphthonitrile, there was evidently an extensive concurrent chlorination to a dichloronaphthonitrile.

Cleve's acid was acetylated to sodium 5-acetamido-2-naphthalenesulfonate which, with phosphorus pentachloride, was transformed into 5-acetamido-2-naphthalenesulfonyl chloride. Treatment of this with aniline yielded 5-acetamido-2-naphthalenesulfonanilide. Similar compounds of 1,4-orientation are described by Schroeter (2), and 5-benzamido-2-naphthalenesulfonyl chloride is reported by Schweitzer and Burr (3).

Chloromethylation of 2-chloronaphthalene was accomplished successfully, but the orientation of the chloromethyl group was not established. We confirmed the statement of Rupe and Brentano (4) that the chloromethyl group in benzyl chloride was convertible to an aldehyde group by heating with hexamethylenetetramine. Correspondingly, α-naphthylmethyl chloride and bromide yielded 21% and 44%, respectively, of 1-naphthaldehyde. The same method should apply with the x-chloromethyl-2-chloronaphthalene, but this work still awaits development.

Our experience with nitration of 2-naphthylamine by the method of Friedlaender and Szymanski (5) failed to check their results. They reported 5-nitro-2-naphthylamine, m.p. 143.5°, as the chief product together with a small amount of 8-nitro isomer, m.p. 103.5°. Our product melted at 91–92°. This points to a predominance of the 8-nitro isomer.

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[1] The work described in this paper was done under contracts recommended by the National Defense Research Committee and the Committee on Medical Research between the Office of Scientific Research and Development and Northwestern University.

Passing mention may be made to another nitration, carried out in the present investigation. This was the conversion of benzyl acetate by a mixture of nitric and sulfuric acids into a 37% yield of *p*-nitrobenzyl acetate. Also obtained was a substantial quantity of oily product which undoubtedly contained the ortho isomer. Beilstein and Kuhlberg (6) nitrated benzyl acetate with cold nitric acid of the highest concentration and also obtained *p*-nitrobenzyl acetate. They listed no yield.

EXPERIMENTAL

I. *Approaches to chloronaphthaldehyde via Gattermann aldehyde synthesis.* Anhydrous hydrogen cyanide (7.4 ml.) was added dropwise during fifteen minutes into a suspension of 20.6 g. of aluminum chloride in 31 ml. of ice-cooled chlorobenzene. After leaving the mixture fifteen minutes at room temperature to form $AlCl_3 \cdot 2HCN$, 10 g. of 2-chloronaphthalene was added. A slow stream of hydrogen chloride was passed in at 20–25° for fifteen minutes, then at 70° for five hours. The mixture was shaken frequently. The dark thick liquid was poured on ice, acidified, steam distilled to remove chlorobenzene, the residue extracted with ether, the ether extract washed with water and then treated with saturated sodium bisulfite solution. The copious precipitate was separated, washed with ether, and decomposed with sodium carbonate solution. The solid aldehyde which separated melted at 82–85°. Crystallizations from dil. alcohol and from hexane gave 2 g. of light yellow aldehyde, m.p. 100–102° corr. This is evidently the unknown 7-chloro-1-naphthaldehyde, since aqueous permanganate oxidized it to 7-chloro-1-naphthoic acid (7), m p. and mixed m.p. 240–242°. Probably the lower-melting 6-chloro-1-naphthaldehyde (8) was present in the mother liquors.

II. *via Cleve's acid,* 5-amino-2-naphthalenesulfonic acid. This acid was obtained from the duPont Company.

(a) *Sodium 5-cyano-2-naphthalenesulfonate.* Cleve's acid (446 g.), dissolved in 1 liter of water containing 80 g. of sodium hydroxide, was diluted with 500 ml. of water and 1 kg. of crushed ice and precipitated by 1 liter of conc'd hydrochloric acid. The suspension was diazotized at 0–5° by the addition of 135 g. of powdered sodium nitrite during three hours. After neutralization to litmus by solid sodium carbonate, it was added during half an hour to a solution of 2.5 moles of cuprous chloride. Temperature was kept at 0–5° by adding ice. After two hours stirring, it was left overnight at room temperature, then 1.5 kg. of sodium chloride was added, and after two hours the precipitated sulfonate was collected and dried in an oven; yield 480 g.

(b) *5-Cyano-2-naphthalenesulfonyl chloride.* Fifty grams of the crude sodium sulfonate was heated by an oil-bath at 130°, for four hours with 70 g. of phosphorus pentachloride, then the mixture was poured on crushed ice, the brown solid was washed by decantation with cold water, ground in a mortar with cold water, filtered off, and dried. The powder was extracted with 200 ml. of benzene, concentrated to 100 ml., diluted with 100 ml. of hexane, and cooled to 0°. The yield of brown crystals, m.p. 149–151°, was 16.6 g. or 33% assuming pure sodium sulfonate. Another crystallization gave yellow crystals, m.p. 151–153° corr. Yields were less if the reaction period was only one hour, and the yield was negligible at room temperature after ten hours.

Anal. Calc'd for $C_{11}H_6ClNO_2S$: N, 5.57. Found: N, 5.86.

(c) *Aniline derivative.* Treatment of the sulfonyl chloride with aniline gave rise to 5-cyano-2-naphthalenesulfonanilide, m.p. 194°.

Anal. Calc'd for $C_{17}H_{12}N_2O_2S$: N, 9.09. Found: N, 9.24.

(d) *Reaction with phosphorus pentachloride at 160°.* Eight grams of 5-cyano-2-naphthalenesulfonyl chloride and 10 g. of phosphorus pentachloride were heated under reflux in an oil-bath at 160–165° for five hours. The mixture was poured on cracked ice, filtered, dried, and crystallized from alcohol. Four grams (66% calc'd as $C_{10}H_6ClCN$) of white crystals was obtained, m.p 99–101°.

Anal. Calc'd for $C_{11}H_6ClN$: N, 7.47.
Calc'd for $C_{11}H_5Cl_2N$: N, 6.31. Found: N, 6.44, 6.46, 6.20.

Hydrolysis. Refluxing of 8.8 g. of the chlorinated naphthonitrile with 10 g. of sodium hydroxide in 15 g. of water and 50 ml. of alcohol for twenty-four hours liberated ammonia in quantity. The alcohol was distilled off and the residue was filtered and acidified (HCl). The product obtained was crystallized from 50% alcohol; yield 6 g., m.p. 190–200°. With a 5-hour refluxing period, 2.4 g. of nitrile gave rise to 0.2 g. of 6-chloro-1-naphthoic acid, m.p. 217°, and 0.5 g. of alkali-insoluble material.

III. *Other reactions with Cleve's acid.* (a) *Acetylation.* Sodium 5-amino-2-naphthalenesulfonate (117 g.), made from 112 g. of Cleve's acid, was treated with 150 ml. of acetic anhydride. Heat was evolved. After one hour at 100° it was cooled and the sodium 5-acetamido-2-naphthalenesulfonate filtered off and rinsed with alcohol; yield, 128 g. (94%).

(b) *5-Acetamido-2-naphthalenesulfonyl chloride.* Ten grams each of the salt from (a) and phosphorus pentachloride were ground in a mortar. The mixture warmed forming a paste which, in fifteen minutes, was added to crushed ice. The solid was ground with water, filtered off, dried, and extracted with ethyl acetate in a Soxhlet. The yield of light tan crystalline material was 3.3 g. It did not melt up to 250°. Analysis was satisfactory for the sulfonyl chloride.

Anal. Calc'd for $C_{12}H_{10}ClNO_3S$: N, 4.94. Found: N, 5.19.

(c) *5-Acetamido-2-naphthalenesulfonanilide.* This derivative was prepared by reaction of the above chloride with aniline. The white crystals from dilute alcohol melted at 215–217° corr.

Anal. Calc'd for $C_{18}H_{16}N_2O_3S$: N, 8.23. Found: N, 8.49.

IV. *via Chloromethylation of 2-chloronaphthalene.* 2-Chloronaphthalene (31.4 g.), 30% formaldehyde (24 ml.), and conc'd hydrochloric acid (41 ml.) were placed in a three-neck flask (300 ml.) equipped with stirrer and funnel. The contents were heated to 60° and held for six hours, during which conc'd sulfuric acid (27 ml.) was added with stirring. Heating and stirring were continued for another twenty-three hours, after which the mixture was cooled and diluted with 85 ml. of cold water. The mixture was extracted with ether, and the extract washed with water, saturated sodium bicarbonate solution, again with water, dried ($MgSO_4$), and filtered through Norit-Celite. Removal of the solvent left 29.0 g. of a thin, light amber oil which crystallized completely when cooled, and partially remelted at room temperature. This oil was distilled at 0.5 mm. to remove 14.1 g. of 2-chloronaphthalene at 65–85° (m p. 54.5–55.5°). Steam was passed through the 14.9 g. of residue to remove traces of the chloronaphthalene, and the residue was taken up in ether. Removal of the solvent yielded 12.0 g. of amber oil. It was distilled at 1 mm.: 0.6 g. up to 120°; 9 4 g. at 120–123°, n_{D}^{25} 1.6434; residue 2.0 g. which solidified. The 9.4-g. sample was x-chloromethyl-2-chloronaphthalene.

Anal. Calc'd for $C_{11}H_8Cl_2$: Cl, 33.65. Found: Cl, 33.75.

V. *via Nitration of 2-naphthylamine.* Friedlaender and Szymanski (5) report the nitration of 2-naphthylammonium nitrate, by adding it slowly to conc'd sulfuric acid at −25°, to yield primarily 5-nitro-2-naphthylamine, m.p. 143 5°, and the 8-nitro isomer, m.p. 103.5°, as by-product. In our repetition of this work, we obtained from 124 g. of the nitrate 86 g. of red crystalline material, m.p. 88–89° from alcohol. Crystallization from benzene brought this m.p. to 91–92°.

Nitration of benzyl acetate. Dropwise addition (stirring) of 12.5 g. of benzyl acetate to a cooled (7°) mixture of conc'd sulfuric and conc'd nitric acids (12.5 ml. each) yielded a 2-layer system. A yellow solid separated on pouring into ice-water. After crystallization from alcohol, its m.p. was 67–71°. Another crystallization yielded *p*-nitrobenzyl acetate, m.p. 76–78°, in 6 g. yield (37%). An oily product, probably the ortho isomer, was in the mother liquors.

Acknowledgment. Microanalyses for C, H, N reported in this paper were performed by Rita L. Pivan and Winifred Brandt. The Cl analysis was carried out by R. J. Sims.

SUMMARY

The Gattermann reaction with 2-chloronaphthalene yields 7-chloro-1-naphthaldehyde, but the 6-chloro isomer seems to be formed as well. Chloromethylation of 2-chloronaphthalene is described.

Cleve's acid was used as an intermediate for the synthesis of several derivatives of 5-cyano-2-naphthalenesulfonic acid and of 5-acetamido-2-naphthalenesulfonic acid.

Nitrations of 2-naphthylamine and benzyl acetate were investigated.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF TORONTO]

FURFURALNITRIMINE

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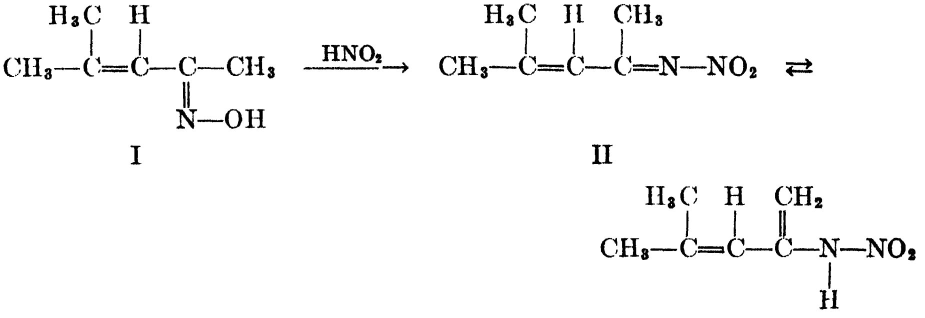
When camphoroxime is treated with nitrous acid, the conversion $R_2CNOH \rightarrow R_2CN_2O_2$ occurs (1), and this was subsequently demonstrated for a number of terpenoid ketones (2, 3, 14, 15, 4, 7, 12). Angeli and his co-workers called these compounds "pernitroso" derivatives and considered them to have structures such as $R_2C{=}N{-}O{-}NO$ or $R_2C{=}(NO)_2$. These oxime nitrite or geminal dinitroso structures were discarded (17) by Scholl in favor of his nitrimine structure $R_2C{=}N{-}NO_2$ when he prepared (18) an analogous compound from pinacolone several months after Angeli's first report. Subsequently Harries and Gley (11) prepared from the oxime of mesityl oxide, I, what Scholl specified as mesityl nitrimine, II, on the basis of Harries' structure proof (10).



$$CH_3-\overset{\overset{H_3C}{|}}{C}=\overset{\overset{H}{|}}{C}-\underset{\underset{N-OH}{\|}}{C}-CH_3 \xrightarrow{HNO_2} CH_3-\overset{\overset{H_3C}{|}}{C}=\overset{\overset{H}{|}}{C}-\overset{\overset{CH_3}{|}}{C}=N-NO_2 \rightleftarrows$$

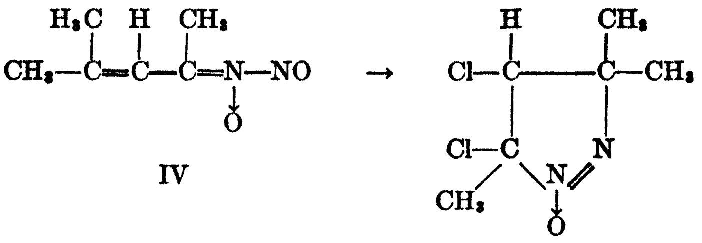
I II

$$CH_3-\overset{\overset{H_3C}{|}}{C}=\overset{\overset{H}{|}}{C}-\overset{\overset{CH_2}{\|}}{C}-\underset{\underset{H}{|}}{N}-NO_2$$

III

He realized that the isomeric nitramine structure, III, was possible, but considered it improbable, since the compounds did not react with phenylisocyanate or diazomethane. Nevertheless, the compounds are soluble (frequently with difficulty) in alkali. This might be expected of III, though not of II. Indeed, Angeli, and also Hantzch and Barth (9), found that the potassium salt of "camphenylnitrimine" yielded a labile isomer, perhaps the nitramine, when acidified. This, however, gradually reverted to the original compound.

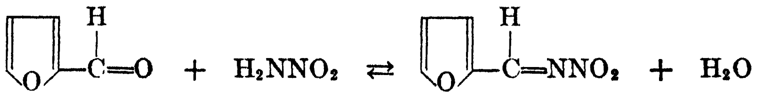
Despite this evidence for nitrimine structure II, convertible to the unsaturated nitramine, Fusco and Trisoglio (8) have proposed an alternative structure IV for the nitrosated mesityloxide oxime on the basis of its conversion with hydrochloric acid to 3,5,5-trimethyl-3,4-dichloro-Δ^1-pyrazoline-2-oxide, V. There is, however, no convincing reason why the product could not be the corresponding 1-oxide, in which case it could quite logically have been derived from the nitrimine II. These workers were perhaps influenced by the fact that oximes of benzaldehyde and furfural will not form nitrimines (13), but principally oxime peroxides. Indeed, an unequivocal demonstration of the nitrimine structure has not been developed.



IV

V

In view of these differences in opinion it seemed worth while to prepare a nitrimine of reliable structure. We have succeeded in preparing furfuralnitrimine by the simple condensation of furfural with nitramide without catalyst or solvent. The reaction would not take place with solvent present. The nitramide probably reacted as such, because it could not be replaced by hyponitrous acid, a possible contaminant.



The compound is unstable toward both acids and bases. The low yield (41% at 0°) resulting when equimolar quantities are used, indicates that a mobile equilibrium exists which is largely in the form of the original reactants. This would explain the sensitivity of furfuralnitrimine to acids and bases, since it would derive these properties from the nitramide to which it could easily revert. This equilibrium was demonstrated by yield increase to 70% with fourfold molar nitramide excess and to 62% with the same molar excess of dry furfural. The addition of furfuralnitrimine to furfural and nitramide depressed the yield expected from these latter reagents. The behavior thus conforms to that expected of a mobile equilibrium.

Furfuralnitrimine is reasonably stable (for a furan) when it is dry and, in fact, is best purified by sublimation at 100°. It decomposes in sodium bisulfite solution to give the aldehyde-bisulfite addition compound. It also decomposes in water, slowly at room temperature, but rapidly above 40° with formation of nitrous oxide and furfural. Addition of sulfamic acid stabilizes the water solution. The compound gives a strong Franchimont (6) test like all the so-called nitrimines and the nitramines, and it reacts in the Liebermann nitrosamine test like all nitramines to give blue-green and blue-violet colors instead of the pure blue given by nitrosamines.

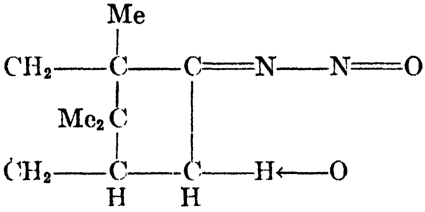
When furfuralnitrimine is treated with phenylhydrazine, a vigorous reaction ensues, and furfural phenylhydrazone is formed. Only 14% of the expected nitrous oxide was isolated. When the same reaction was carried out with camphornitrimine, a colorless, non-oxidizable gas was evolved more slowly than with furfuralnitrimine, but after fifteen minutes, 72% of the theoretical quantity had evolved. The residual oil was shown to be camphor phenylhydrazone by conversion to its picrate.

This hydrazone formation must follow the course

$$R_2C{=}NNO_2 + H_2NNHC_6H_5 \rightarrow R_2C{=}NNHC_6H_5 + N_2O + H_2O$$

and is not unprecedented (16) since hydrazine hydrate will form the corresponding camphorazine. The action of hydrazine hydrate on furfuralnitrimine is, however, much too violent to be useful, while the reaction with phenylhydrazine is controllable. Furthermore, the absence of nitric oxide has more significance when phenylhydrazine is used rather than hydrazine hydrate. Either reagent does, however, demonstrate that the compound with which it reacts is not a primary nitramine, since the latter type of compound will react to form simple salts with phenylhydrazine.

The similarity in behavior of camphornitrimine, prepared from an oxime and nitrous acid, with an authentic nitrimine such as furfuralnitrimine supports Scholl's viewpoint, so far as camphornitrimine is concerned. Furfuralnitrimine has no enolizable hydrogen. Its greater instability compared with a compound like camphornitrimine may be owing to the stabilizing effect of a hydrogen bridge in the latter compound, VI.



VI

On the basis of the present work, Scholl's generalization concerning nitrimines cannot be applied either to his own compound, pinacoline-nitrimine, or Harries' mesityloxide-nitrimine, II. Neither of these compounds evolved gas, even when warmed to 80°, with phenylhydrazine.

No other aldehyde or ketone was found to condense with nitramide. Benzaldehyde, thiophenaldehyde, cinnamaldehyde, mesityloxide, salicylaldehyde, butyraldehyde, and heptaldehyde were all recovered unchanged under the same reaction conditions which produced furfuralnitrimine. These failures were probably not owing to a catalytic effect since a trace of furfural did not effect the condensation of mesityl oxide with nitramide, nor did a trace of mesityl oxide decrease the amount of furfuralnitrimine formation in a certain time. Possible catalytic effects of acid or peroxide were also excluded, although acid is otherwise deleterious because it destroys the nitramide unless the temperature is well below 0°. For the same reason, bases like pyridine cannot be used at any temperature.

Camphor was also treated with nitramide, and no reaction occurred, but this cannot be considered conclusive since the reaction had to be carried out in ether as a solvent. Under these conditions, furfural would not react with nitramide.

EXPERIMENTAL

Mesitylnitrimine. The preparation of Harries was repeated in 57% yield. The purified compound, m.p. 141–142°, gave a green Franchimont test with dimethylaniline and a green-blue Liebermann test. It was not soluble in cold sodium hydroxide, but it dissolved on warming without decomposition.

d-Camphornitrimine. The method of Angeli gave yields of 62–70%. The compound dissolves readily in dilute potassium hydroxide without decomposition, and forms the yellow potassium salt melting at 43°.

Pinacolinenitrimine. Pinacolonoxime, 4.6 g. (0.04 mole), was dissolved in 50 ml. of dry ether and treated with 4.6 g. (0.05 mole) of freshly distilled, liquid N_2O_4 at ice-salt temperatures. After standing 45 hours, the green liquid was separated from the precipitated ammonium nitrate and was washed three times with 5 ml. of 2% aqueous sodium hydroxide solution. After drying the ethereal layer with calcium chloride, vacuum fractionation gave 1.8 g. (32%) of pinacoline-nitrimine boiling at 80–83°/11 mm. A Franchimont test was positive, as was a Liebermann nitroso test. A little of the oil was insoluble in cold dilute potassium hydroxide but formed the salt with conc'd aqueous alkali on warming.

Furfuralnitrimine. The heart-cut from three repeated distillations of furfural insured a pure dry material. Nitramide was prepared by the method of Booth (5) and was used immediately while it melted at 72–73°, and before it turned brown in color. To 0.38 g. (0.004 mole) of furfural at 0° was added 0.25 g. (0.004 mole) of nitramide, which dissolved almost immediately. The mixture solidified gradually during fifteen hours at 0°. The product was dissolved by addition of 10 ml. of dry acetone. This was vacuum evaporated into the bottom of a test tube. The residue was washed on to a suction filter with 2.5 ml. of ice-water and dried at 50°, weight 0.18 g. or 35% yield, m.p. 114°. If the reaction mixture was washed directly on to a suction filter with water, the added washing (15 ml.) necessary to remove excess furfural reduced the yield to 31%, m.p. 115–116°. This unused furfural could however be removed by distillation at 25°/0.001 mm., and the yield thus raised to 42%, m.p. 114°.

This distillation was necessary when four moles of furfural was treated with one mole of nitramide. The distillation at 0.0005 mm. was carried out after three hours' reaction time to leave a residue which was crystallized from warm benzene to give a yield of 62%, m.p. 116°.

An excess of four moles of nitramide per mole of furfural at 0°, gave after eight hours a 72% yield by the water-washing technique, m.p. 115°.

When one mole of nitramide, one mole of furfural, and 0.5 mole of furfuralnitrimine were let stand at 0° for eleven hours, the yield, after deducting the original addend, was only 21%.

No furfuralnitrimine was obtained when water-wet furfural was used in the reaction. When benzene was used as the reaction solvent, the yield was decreased to 5% after eighteen hours at 0°.

The presence of acid traces like acetic acid and hydrogen chloride did not affect the yield if the temperature was low enough to avoid decomposition of the nitramide. Peroxides like ascaridole likewise had no effect, nor did nitrous oxide. Pyridine in trace destroyed the nitramide immediately. Furfural diacetate would not replace furfural in this reaction.

The effect of temperature on reaction rate using equimolar quantities of furfural and nitramide is tabulated for a series of experiments all processed identically to give products m.p. 114–116.5°.

Furfuralnitrimine is soluble in warm benzene and ethanol and very soluble in cold acetone or methyl ethyl ketone. It may be purified by crystallization from warm benzene to yield straw-colored wedge-shaped crystals, m.p. 116.5°, or sublimed at 100°/10 mm. to melt at 117°. The Barger-Rast molecular weight in acetone was found to be 130 (calc'd 140).

Anal. Calc'd for $C_5H_4N_2O_3$: C, 42.9; H, 2.86; N, 20.0.
Found: C, 43 2; H, 2.81; N, 20.0.

Hydrolysis of furfuralnitrimine. A 0.1-g. sample was shaken with 1 ml. of distilled water for twelve hours, forming a completely clear solution with no residual solid. The *p*H was 5.4 compared with 5.5 for the original distilled water. Spot plate tests for nitric acid by the "brown-ring" reaction and with brucine in dilute sulfuric, showed no nitrate ion. A poor test for nitrous acid was obtained with a drop of sulfanilic acid and α-naphthylamine; only a pale pink color appeared after standing. The addition of phenylhydrazine to the hydrolysate resulted in the precipitation of fine orange crystals of furfuralphenylhydrazone (m.p. 97°).

Furfuralnitrimine on warming with a little water begins to evolve gas at about 40° with decomposition of all the solid present.

Nitrimines with phenylhydrazine. Pernitrosocamphor (m.p. 43°), 0.02 g. (0.0001 mole) was placed in a small test tube with 0.022 g. (0.0002 mole) of freshly distilled phenylhydrazine, taking care not to mix the reagents. The tube was then connected to a calibrated gas burette and tilted so that the reagents combined in a closed system. No gas evolution was at first noticeable but after fifteen minutes at room temperature (25°) the burette showed 1.8 ml. of gas, 72% of the theoretical quantity. To the reaction mixture, an orange-brown oil, was added an equivalent volume of ethanol and then alcoholic picric acid. The golden-yellow needles which formed melted at 137° and a mixed melt with authentic *d*-camphor phenylhydrazone picrate gave no depression of the melting point.

TABLE I

EFFECT OF TEMPERATURE ON REACTION RATE

TIME IN HRS.	% YIELD OF FURFURALNITRIMINE		
	−18°	−10°	0°
0.25	2.0	6.7	25
0.5	2.8		
2	17		
3			44
4.5	28		
22			44
48	35		
75	36		

TABLE II

SOLUBILITY OF NITROUS OXIDE IN FURFURAL

TEMPERATURE °C.	G N_2O 100 G. FURFURAL	ML. N_2O 100 G. FURFURAL
30	5.0	280
15	6.1	325
0	7.7	390

Similarly, 0.001 g. (7×10^{-6} moles) of furfuralnitrimine was combined with 0.0015 g. (14×10^{-6} moles) of phenylhydrazine at 29°; after eight minutes, 0.25 ml. of the quickly evolved gas was recorded (14%). Reabsorption of some of the nitrous oxide produced was noticed and since it is very soluble in any furfural present this might account for the low yield of gas evolved. The addition of a little warm 50% alcohol-water subsequently gave red-brown crystals (m.p. 97°) which were identified by a mixed melt with an authentic sample of furfural phenylhydrazone.

The solubilities in Table II were determined by saturation of furfural at the given temperature until no further change in weight occurred.

Qualitative color tests with nitrimines. When Franchimont tests were carried out on mesitylnitrimine, pinacolinenitrimine, pernitrosocamphor, and furfuralnitrimine, a green color which rapidly faded was obtained with dimethylaniline. The ruby color obtained with α-naphthylamine in this test was more permanent. In the Liebermann nitroso reaction, a known nitroso compound gave a pure deep blue color. Mesitylnitrimine on trial gave a dark green color, while pernitrosocamphor, pinacolinenitrimine, and furfuralnitrimine gave greenish-blue to violet-blue shades.

Acknowledgment. One of the authors (G. S. M.) is grateful for a grant-in-aid from the National Research Council.

SUMMARY

A true nitrimine has been prepared from furfural and nitramide. It resembles camphornitrimine in its properties but it behaves differently from the compounds reported as mesitylnitrimine and pinacolylnitrimine.

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APPLICATION OF THE DARZENS-CLAISEN REACTION TO A β-DIALKYLAMINO KETONE[1]

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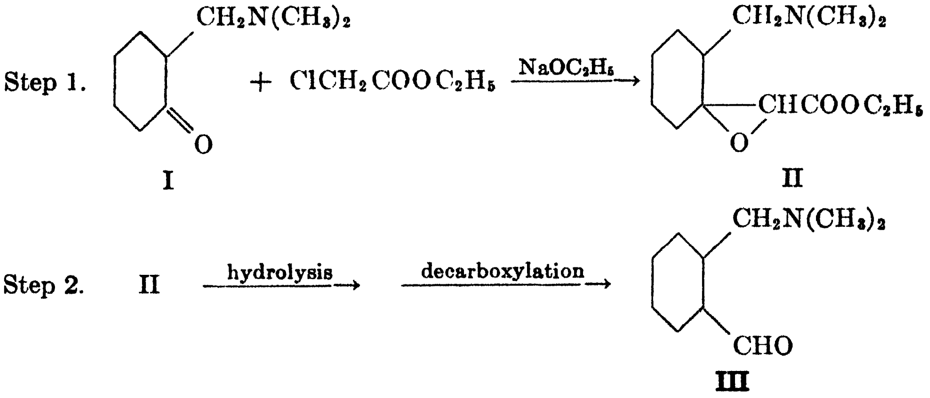
Several years ago a convenient synthesis of 1,3-disubstituted γ-piperidones was developed in these Laboratories (1). The present research was prompted by an interest in methods which might be employed to convert such a piperidone into homomeroquinene.[2] Provided the processes discovered independently by Darzens (4) and by Claisen (5) could be applied to ketones of the γ-piperidone type,[3] one might attach a formyl group to the ketonic carbon of the piperidone and proceed by conventional methods to homomeroquinene or a suitable derivative [*cf.* (2)].

Model β-dialkylamino ketones which could be used in exploring the applicability of the Darzens-Claisen method to our problem are readily provided by the well-known Mannich reaction; the simplest ketone of this type, derived from acetone by the action of dimethylamine and formaldehyde, was abandoned in favor of 2-dimethylaminomethylcyclohexanone (I), similarly derived from cyclohexanone, but in much better yield.

The two steps of the Darzens-Claisen process are illustrated below as applied to the model (I).



Yields of 43–57% of the desired basic glycidic ester (II) were obtained following the simple directions originally published by Darzens (4). The product of the condensation (step 1) was a mixture of two diastereoisomeric esters (II)[4] which were separated by fractional recrystallization of their dilituric-acid salts.

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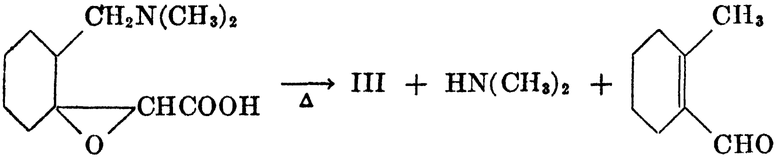
[1] The contents of this paper were presented before the Pacific Division of the American Association for the Advancement of Science at the Reno, Nevada meeting, June 19, 1946.

[2] Work on this important intermediate in the synthesis of quinine (2, 3) was interrupted by other investigations of synthetic antimalarial drugs suggested by the Committee on Medical Research; the Woodward-Doering synthesis (3) having appeared in the mean time, we are terminating our work on this problem with this communication.

[3] Clemo and co-workers (6) used this method to obtain a glycidic ester from a basic ketone, but were unable to prepare the desired aldehyde from the ester.

Refluxing the esters (II) for thirty minutes with concentrated hydrochloric acid gave the desired basic aldehyde (III) in 15% yield; and since it was shown that both the pure isomeric esters (regenerated from the diliturates) gave the same aldehyde[5], the crude mixture served as well for its preparation.

Small amounts of III were also obtained by thermal decomposition of the basic glycidic acids (IV) obtained from II by saponification with barium hydroxide, but the principal products of this reaction were identified as dimethylamine and a non-basic aldehyde tentatively formulated as 2-methyl-3,4,5,6-tetrahydrobenzaldehyde (V);[6] the deep scarlet color of the 2,4-dinitrophenylhydrazone of this aldehyde is in agreement with its postulated conjugated configuration.[7]



IV V

The basic aldehyde (III) is apparently stable when stored under nitrogen, but on exposure to air a crystalline compound is rapidly formed, the properties and composition of which are compatible with those expected of *o*-dimethylaminomethylhexahydrobenzoic acid.

The author wishes to thank Dr. Edwin R. Buchman for suggesting this problem and for guidance throughout its execution.

EXPERIMENTAL[8]

2-Dimethylaminomethylcyclohexanone (*I*) was prepared by the method of Mannich and Braun (10) in yields which seemed to depend on the size of the run; a one-mole experiment gave 71%, three-mole 64.3%, and 6.13-mole 55.2% of colorless, mobile oil boiling at 96–97° at 11.5 mm. [Dimroth, Resin, and Zetzsch (11) give b.p. 93–94° at this pressure]. Contrary to statements of Mannich and Braun, we did not find I to be unusually unstable; redistillation of a sample which had stood at room temperature for almost three years gave a 75% recovery of the basic ketone.

The hydrochloride of I, recrystallized once from ethyl acetate and again from isopropyl ether-ethanol, formed small, glistening, white flakes melting at 139.9–140.6° when heated slowly; the melting point was somewhat higher (145.5°) when the bath temperature was raised more rapidly (Mannich and Braun give m.p. 152°).

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[4] Four diastereoisomers are theoretically possible; Miescher and Kägi (7) were able to isolate derivatives of four different glycidic acids derived by a somewhat similar process from an asymmetrically-substituted, *non-basic* cyclopentanone (dehydroandrosterone).

[5] This fact must not be taken to indicate that the cis-trans configurations of the cyclohexane-substituent C—C bonds in the two esters are the same, since the degradation (step 2) in aqueous acid probably involves the intermediate formation of the enolic modification of the aldehyde, tautomerism yielding the more stable (probably trans) aldehyde.

[6] Without any proof of structure, Wallach (8) assigned this configuration to an aldehyde prepared by an ambiguous method.

[7] See generalization formulated in these Laboratories by Dr. C. E. Redemann, cited by Buchman *et al.* (9).

[8] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and her staff of this Institute and by the Huffman Microanalytical Laboratories, Denver, Colorado.

Anal. Calc'd for $C_9H_{18}ClNO$: C, 56.39; H, 9.46; N, 7.31.
Found: C, 56.69; H, 9.25; N, 7.25.

Mannich and Braun claim to have been unable to prepare the methiodide of I because of its instability; Dimroth and his co-workers prepared the salt in ether solution under nitrogen and reported it stable in the pure crystalline form, m.p. 136–137°, followed by resolidification and decomposition from 200°. We prepared the salt using no special precautions and obtained a product forming, from ethanol, clusters of colorless pyramids in square patterns, m.p. 152–153°, resolidifying at about 160°.

Anal. Calc'd for $C_{10}H_{20}INO$: C, 40.41; H, 6.78; N, 4.71.
Found: C, 40.78; H, 6.83; N, 4.80.

Prepared by adding isopropyl-ethereal picric acid to a solution of I in the same solvent, the picrate formed minute yellow needles from isopropyl ether-ethanol, m.p. 147.0–147.2° (Mannich and Braun give m.p. 149°).

Attempts to apply the Reformatsky reaction (with zinc and methyl bromoacetate) to I were apparently complicated by quaternary salt formation, giving only traces of starting material and negligible amounts of higher-boiling basic substances.

Dimethylaminomethylacetone was obtained in yields of 3.6 to 13% following the directions of Mannich (12); careful fractional distillation was required to purify the base, b.p. 50–51° at 13 mm., in agreement with Mannich. A small sample of this material subjected to the Darzens-Claisen condensation (see details below) gave 6.1% of the starting material and 4.7% of a pale yellow, viscous oil boiling at 78–91° at 3 mm. An attempt to condense this ketone with ethyl dichloroacetate in the presence of a magnesium amalgam [*cf.* (13)] gave a negligible yield of high-boiling material.

2-Carbethoxy-4-dimethylaminomethyl-1-oxaspiro[2.5]octane [*cf.* (14)(II)]. A mixture of 77.6 g. (0.5 mole) of I and 61.25 g. (0.5 mole) of ethyl chloroacetate was cooled in a three-necked 500-cc. flask equipped with a mercury-sealed Hershberg stirrer, a water-cooled Allihn condenser protected by a calcium chloride tube and containing a thermometer dipping into the mixture, and a small conical flask attached to the third neck by a piece of large-bore rubber tubing and containing 34.0 g. (0.5 mole) of freshly-prepared, dry, alcohol-free sodium ethoxide (15). The ethoxide was slowly added at such a rate that the temperature of the mixture did not exceed 20°, requiring about thirty minutes.[9] After stirring overnight at room temperature the light brown paste was heated in a boiling-water bath for three hours, during which it first thickened, then became more mobile and somewhat lighter in color. This paste was cooled in ice, dissolved in 160 cc. of cold 6 *N* hydrochloric acid, washed with ether, carefully basified with potassium hydroxide, and the liberated red-brown oil extracted with two 200-cc. portions of ether; dried over sodium sulfate and stripped of ether, the product was distilled at 0.025 mm. (gauge pressure), yielding 64.4 g. (53.3%) of light yellow oil, b.p. 101–110°. A one-mole run in which the temperature of the mixture was kept under 0° during the addition of the ethoxide gave a 53.8% yield of II, b.p. 110–115° at 1 mm. Other experiments gave yields ranging from 43.5 to 57.5%. For analysis, a sample of II was redistilled at 3 mm., b.p. 127-129°.

Anal. Calc'd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81.
Found: C, 64.45; H, 9.60; N, 6.03.

Separation of isomeric esters (II) with dilituric acid. One-tenth mole (24.1 g.) of the above ester mixture was dissolved in 300 cc. of absolute ethanol and 22.7 g. (0.1 mole) of dilituric acid trihydrate was added; the mixture was brought to a boil and water added dropwise as long as solid continued to dissolve; a trace of difficultly-soluble white solid was then filtered off. On cooling, 24.7 g. of the α-form of II diliturate crystallized out as small, compact clusters of light yellow plates; this crop was filtered off, washed with ethanol and isopropyl ether, and air-dried. After standing for about a week, the mother liquors deposited 7.1 g. more of the same material. Spontaneous evaporation of a small portion of the first-crop mother liquors gave seed crystals of the β-diliturate, which were added to the mother liquors from the second crop of the α-diliturate, yielding 3.8 g. of the β-form, compact white needle clusters. Evaporation of the filtrate from this crop to dryness left 13.3 g. of material whose melting point could not be raised above 133–134° by repeated recrystallization from ethyl acetate-ethanol, but which gave on regeneration a poor yield of β-II, identified by the methiodide and diliturate (see below).

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[9] As an orienting experiment, these same conditions were applied to cyclohexanone itself (16), giving a 76% yield of 2-carbethoxy-1-oxaspiro[2.5]octane [*cf.* (14)], b.p. 106–112° at 6 mm. [lit. (16), b.p. 128-129° at 17 mm.]; this was saponified with aqueous potassium hydroxide to give the corresponding acid (yield 90%), clusters of short, colorless needles from water, m.p. 125.0–125.7°, analysis for $C_8H_{12}O_3$.

The α-II diliturate, recrystallized from ethanol-water, melted at 188.6–188.8° dec. After several recrystallizations from ethanol, the β-II diliturate formed clusters of colorless needles with a greenish tinge, m.p. 177.2–178.0° dec.

Anal. Calc'd for $C_{17}H_{26}N_4O_8$: C, 49.27; H, 6.33; N, 13.52.
Found (α-form): C, 49.60; H, 6.25; N, 13.32.
(β-form): C, 49.63; H, 6.46; N, 12.76.

Characterization of pure α-II. A suspension of 10.4 g. of finely-powdered α-II diliturate in 50 cc. of water was warmed just sufficiently to dissolve the salt, cooled in ice, and treated with 7.51 g. (one equivalent) of freshly-distilled anhydrous ethylenediamine [see (17)]; the diamine diliturate was centrifuged down and the crude ester (α-II) (more dense than the aqueous solution) extracted with ether, dried over potassium carbonate, and distilled; yield 3.54 g. (60%) of colorless, very viscous oil, b.p. 95–98° at 1 mm. An aqueous solution of α-II diliturate basified with 4 *N* sodium hydroxide and extracted with ligroin gave 75.5% of α-II, undistilled. A portion of the distilled product was analyzed.

Anal. Calc'd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81.
Found: C, 64.61; H, 9.68; N, 5.58.

The basic glycidic acid (α-IV) was obtained by boiling 1.21 g. of pure α-II with 50 cc. of saturated aqueous barium hydroxide for fifteen minutes, a clear solution resulting in five. Careful precipitation of the barium with 6 *N* sulfuric acid followed by evaporation to dryness gave 1.00 g. of colorless solid which, after washing with acetone, melted at 188–190° dec. One recrystallization from acetonitrile-methanol gave very tiny colorless granules, m.p. 202–203° dec.

Anal. Calc'd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57.
Found: C, 61.83; H, 8.71; N, 6.42.

Addition of one equivalent of methyl iodide to the ester (α-II) or a concentrated ethanolic solution of it gave the α-II methiodide, which crystallized in either of two forms of different melting point. One form emerged from ethanol in massive clusters of colorless prisms with pyramidic terminations or as diamond-shaped plates thickening into rhomboid figures, m.p. 186.9–187.3°. The other, also recrystallized from ethanol, formed colorless, irregularly-faced, acute pyramids melting at 217.3–218.1°; from ethyl acetate-ethanol, feathered pyramids of m.p. 220.1–220.4° were noted. The form obtained in the absence of seed crystals seemed to be a matter of chance; a warm ethanolic solution of the lower-melting seeded with the higher-melting form gave the latter on cooling.

Anal. Calc'd for $C_{14}H_{26}INO_3$: C, 43.87; H, 6.84; N, 3.65.
Found (187°): C, 44.09; H, 6.87; N, 3.17.
(218°): C, 44.26; H, 6.71; N, 3.56.

Prepared in the same way, the ethiodide of α-II crystallized from ethyl acetate-ethanol in beautiful clusters of colorless, stubby needles, m.p. 187.6–188.0°. A mixture of this salt with the lower-melting methiodide (above) had m.p. 186–195°.

Anal. Calc'd for $C_{15}H_{28}INO_3$: C, 45.34; H, 7.10; N, 3.53.
Found: C, 45.47; H, 7.52; N, 3.35.

Treatment of α-II with isopropyl-ethereal oxalic acid gave a colorless oil which solidified on standing; after four recrystallizations from isopropyl ether-ethanol, the white rosettes so formed melted at 140.9–141.7° and analyzed as the acid oxalate.

Anal. Calc'd for $C_{13}H_{23}NO_3 \cdot C_2H_2O_4$: C, 54.36; H, 7.60; N, 4.23.
Found: C, 54.15; H, 7.60; N, 4.46.

Addition of isopropyl-ethereal solutions of picric and 3,5-dinitrobenzoic acids to α-II gave oily precipitates.

Characterization of pure β-II. By the ethylenediamine method detailed above, 3.8 g. of the crude β-II diliturate yielded 1.01 g. (48%) of pure β-II, very viscous, colorless oil, b.p. 93–94° at 1 mm. Liberation of the free base with aqueous sodium hydroxide gave a yield of 43%, undistilled.

Anal. Calc'd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.81.
Found: C, 64.88; H, 9.62; N, 5.63.

By the method described above, the acid (β-IV) was obtained in quantitative yield, crude m.p. 196° dec.

β-II methiodide formed clumps of colorless granules from ethanol, m.p. 173.4–173.6°.

Anal. Calc'd for $C_{14}H_{26}INO_3$: C, 43.87; H, 6.84; N, 3.65.
Found: C, 43.37; H, 7.21; N, 3.53.

Recrystallized from isopropyl ether- or ethyl acetate-ethanol, the ethiodide of β-II formed clusters of fine colorless needles or blades with a micaceous luster, m.p. 134.9–135.3°.

Anal. Calc'd for $C_{15}H_{28}INO_3$: C, 45.34; H, 7.10; N, 3.53.
Found: C, 45.37; H, 6.97; N, 3.13.

The picrate of β-II was obtained as a red oil which could not be induced to crystallize.

o-Dimethylaminomethylhexahydrobenzaldehyde (III). One-eighth mole (30.2 g.) of the ester mixture (II) was treated with 104 cc. of 12 *N* hydrochloric acid and refluxed for one-half hour, giving a deep wine-red, slightly cloudy solution and a small amount of dark green oil. After cooling in ice, the solution was basified by the slow addition of 30% aqueous potassium hydroxide, the solution turning yellow at about the neutral point. The product was extracted with isopropyl ether (freshly-distilled), dried over potassium carbonate, and distilled at 1 mm., yielding 3.20 g. (15.2%) of colorless liquid boiling at 61.6–62.3°; about an equal amount of brown oil remained in the boiler. The aldehyde (III) had a characteristic terpene-like odor, was insoluble in water, and was fairly stable when not exposed to the air (see below).

Anal. Calc'd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28.
Found: C, 71.11; H, 11.30; N, 8.32.

Small amounts (2.2 and 1.1 g., respectively) of the pure esters (α- and β-II) subjected to this same procedure gave the same aldehyde (III), identified in the case of the α-ester as the picrate, in that of the β-ester as the air-oxidation acid; these derivatives are described below.

Hydrolysis of another one-eighth mole of the mixed esters (II) with 500 cc. of 1.68 molar sulfuric acid, refluxing overnight, gave 0.79 g. (3.7%) of III.

On cooling a solution of the picrate of III in hot ethanol-acetonitrile, the salt emerged as dendritic, bright yellow needle-clusters which slowly changed into larger, darker yellow blades; both forms had the same melting point (168.6–169.4°), which was not depressed by admixture.

Anal. Calc'd for $C_{16}H_{22}N_4O_8$: C, 48.23; H, 5.57; N, 14.06.
Found: C, 48.30; H, 5.82; N, 13.68.

The methiodide of III, prepared in ethanol and recrystallized from ethyl acetate-acetonitrile, formed irregular clusters of colorless bars, m.p. 213.8–214.0°; this melting point was somewhat higher when the heating was rapid.

Anal. Calc'd for $C_{11}H_{22}INO$: C, 42.45; H, 7.13; N, 4.50.
Found: C, 42.58; H, 7.07; N, 4.27.

An attempt to prepare the 2,4-dinitrophenylhydrazone of III by the usual method (18) gave instead the hydrochloride of the desired derivative, clusters of light or orange-yellow needles from acetonitrile, m.p. 221.5–221.8° dec.

Anal. Calc'd for $C_{16}H_{24}ClN_5O_4$: C, 49.81; H, 6.27; N, 18.16.
Found: C, 50.36; H, 6.50; N, 18.44.

Basifying an aqueous solution of this salt with aqueous sodium hydroxide gave the free

2,4-dinitrophenylhydrazone, also recrystallized from acetonitrile, beautiful clusters of light orange rods, m.p. 146.9–147.4°.

Anal. Calc'd for $C_{16}H_{23}N_5O_4$: C, 55.00; H, 6.63.
Found: C, 55.28; H, 6.36.

Attempts to prepare the semicarbazone of III were unsuccessful.

Exposure of III to air resulted in the rapid deposition of colorless bobbin-clusters, apparently *o*-dimethylaminomethylhexahydrobenzoic acid; washed with ligroin or isopropyl ether and recrystallized from ethyl acetate-ethanol, this compound melted at 154–155°; it was readily soluble in water, giving a weakly basic solution (*p*H about 8).

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56.
Found: C, 64.24; H, 10.37; N, 7.60.

When this acid was stirred with an ethereal solution of diazomethane at 0°, the acid slowly dissolved, nitrogen was evolved, and a white flakey solid separated from the solution. Evaporation of the ether and excess diazomethane left a colorless oil. This was treated with isopropyl-ethereal picric acid, giving a red oil which solidified on standing and scratching; recrystallized from isopropyl ether-ethyl acetate, the picrate of the methyl ester formed rugged orange bipyramids, m.p. 114–115° after some softening from 112°.

Anal. Calc'd for $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.65; N, 13.08.
Found: C, 47.80; H, 5.69; N, 13.04.

Thermal decomposition of the basic glycidic acids (IV), derived as described above from the mixed esters (II), was accomplished by heating to 200° in a vessel evacuated to 1 mm.; a vigorous evolution of gases ensued, leaving a frothy, tan solid which was extracted with isopropyl ether and treated with picric acid in the same solvent; the picrate thus obtained was identified as that of III by m.p. and mixed m.p.

In a similar experiment with an 0.83-g. sample of α-IV, about 0.4 cc. of a light yellow-green liquid was trapped out with dry ice; redistillation of this material gave 0.2 cc. of colorless oil, b.p. *ca.* 80° (bath temperature) at 4 mm. This oil gave a 2,4-dinitrophenylhydrazone, deep scarlet needles from acetonitrile, m.p. 192.4–192.7°, analyzing as that of 2-methyl-3,4,5,6-tetrahydrobenzaldehyde (V).

Anal. Calc'd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18 41.
Found: C, 55.45; H, 5.13; N, 18.88.

Another portion of this redistilled product derived from α-IV gave a picrate, yellow needles from isopropyl ether-ethanol, m.p. 147.8–148.1°, in amount too small for analysis.

The crude product trapped out in another thermal decomposition of a sample of α-IV was treated directly with isopropyl-ethereal picric acid; the crude picrate was recrystallized from isopropyl ether-ethanol, giving a mixture of yellow needles and red blades which were separated mechanically. The yellow needles crystallized in clusters from ethanol, m.p. 193.4–193.9° to a black liquid, found: C, 49.49, 49.71; H, 5.07, 5.37; N, 15.80, 15.66. The red blades formed orange lattices from ethanol, m.p. 159.9° after some sintering from 155°, unaffected by admixture with an authentic sample of dimethylamine picrate [Jerusalem (19) gives m p. 158–159°].

Anal. Calc'd for $C_8H_{10}N_4O_7$: C, 35.04; H, 3.68; N, 20.43.
Found: C, 35.30; H, 3.73; N, 20.21.

A 0.47-g. sample of β-IV thermally decomposed in the same way gave, on redistillation of the trapped-out material, 0.07 g. of a colorless oil having a strong terpene-like odor and boiling at 66–76° at 10 mm.; the picrate prepared from this oil could not be induced to crystallize, but the 2,4-dinitrophenylhydrazone formed deep scarlet needles or bars from acetonitrile, m.p. and mixed m.p. identical with that of the derivative similarly obtained from α-IV (see above), presumably of V.

SUMMARY

The Darzens-Claisen reaction has been applied successfully to the conversion of a typical β-dialkylamino ketone into a mixture of two basic glycidic esters;

these have been separated as their dilituates and degraded to the same basic aldehyde.

PASADENA 4, CALIFORNIA

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[Contribution from Noyes Chemical Laboratory, University of Illinois]

SOME DERIVATIVES OF OXANILIDE[1]

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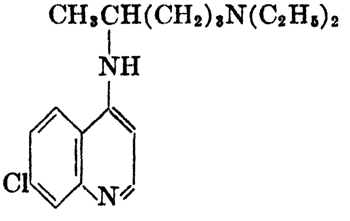
Received November 18, 1946

The high antimalarial activity of the drug known as SN-7618, 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (I), suggested the desirability of preparing and testing some biquinolyl analogs such as II.



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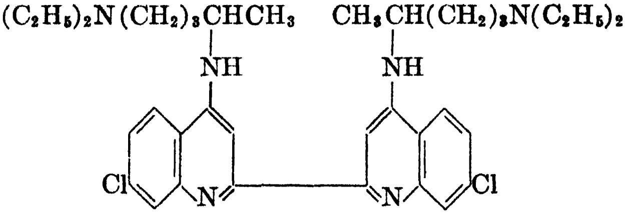

II

It was hoped that the synthesis of II might be accomplished through a modification of the procedure recently reported for the synthesis of I (1). *m*-Chlorooxanilide (III) was converted to the imidochloride (IV) which was then coupled with sodiomalonic ester to yield the expected product (V) in poor yield, plus a by-product (VI). V is structurally similar to the α-carbethoxy-β-anilinoacrylates which were so successfully cyclized to 4-hydroxyquinoline derivatives by boiling in diphenyl ether or Dowtherm (1). As for the simpler analogs, heating in diphenyl ether resulted in the loss of alcohol, but three equivalents, rather than the expected two, were lost in the reaction, to give a product which may have the structure VII. On boiling with alkali this material lost the elements of alcohol, *m*-chloroaniline, and carbon dioxide to yield an acid which gave analytical values for VIII.

The structure assigned to compound VI could arise from replacement of only one chlorine atom of IV with malonic ester followed by hydrolysis to the hypothetical intermediate XI and cyclization with loss of ethanol.

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[1] The work described herein was carried out in part under contract OEMsr-593, recommended by the National Defense Research Committee, and in part under a contract, recommended by the Committee on Medical Research, both between the Office of Scientific Research and Development and the University of Illinois.

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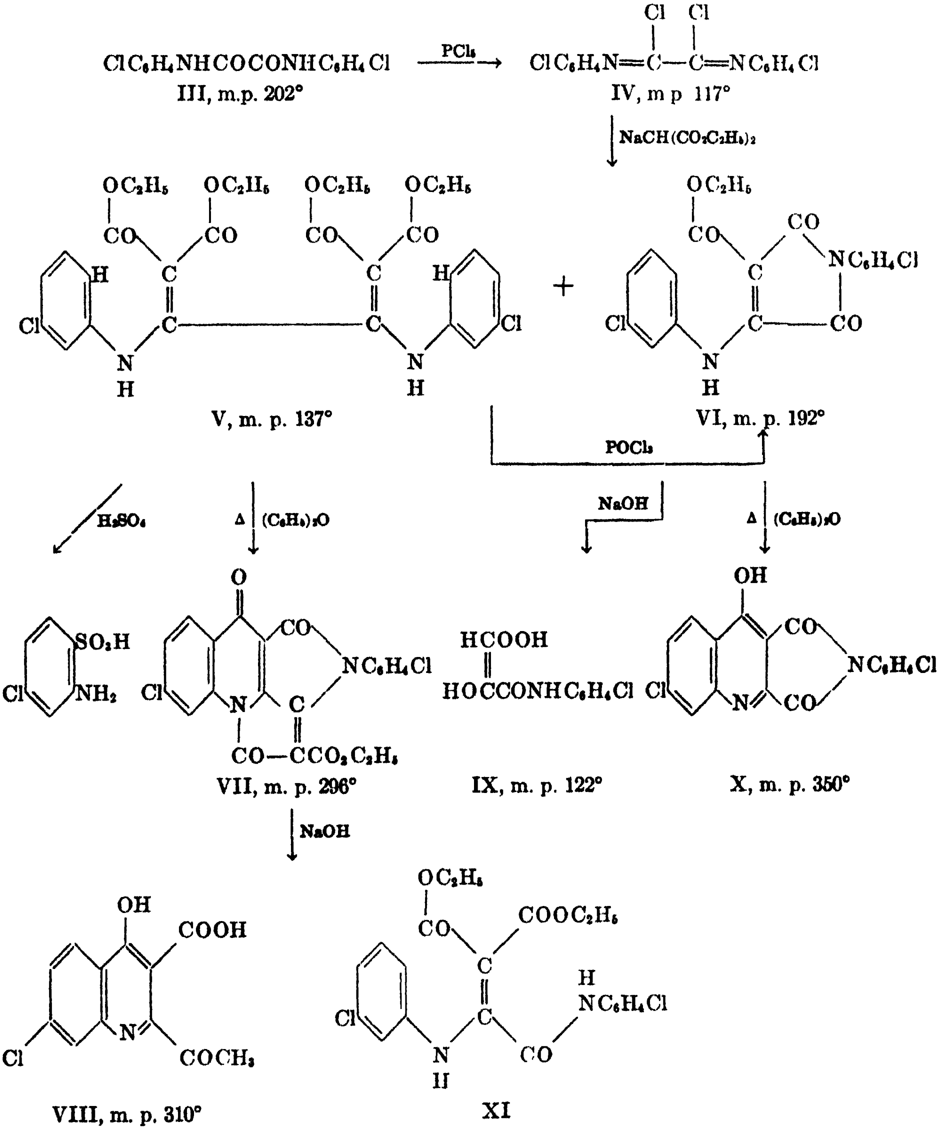
Structure VI is based principally on the analytical data and alkaline hydrolysis



to compound IX which appears to be identical with a substance of this structure, m.p. 122–123°, recently described by Surrey and Cutler (2, 3).

In view of the reported (4) thermal cyclization of half anilides of malonic ester to quinoline derivatives, the *m*-chloro derivative (XII) was prepared and heated under the prescribed conditions. In this case, the only product was the *bis-m*-chloroanilide.

$$\underset{\text{XII, m. p. }76^\circ}{C_2H_5O_2CCH_2CONHC_6H_4Cl} \xrightarrow{250^\circ} \underset{\text{m. p. }166^\circ}{CH_2(CONHC_6H_4Cl)_2}$$

For a different purpose, it seemed of interest to evaluate certain dithiooxanilides as potential reagents for detection or analysis of certain metal ions. Although this objective was not achieved, *p,p'*-dinitrooxanilide and *p*-dimethylamino-*p'*-nitrooxanilide and the imidochloride derivative of the former were prepared and characterized.

EXPERIMENTAL[4,5]

Preparation of m,m'-dichlorooxanilide. A mixture of 31.9 g. (0.25 mole) of *m*-chloroaniline and 19.0 g. (0.13 mole) of ethyl oxalate was heated to 120° in an open beaker on a hot-plate. Approximately one gram of metallic sodium (5) was added slowly in small pieces with stirring. After fifteen minutes, the mixture became slushy and was removed from the hot-plate. When cooled, the completely solidified mixture was boiled with ethanol and filtered. A small amount was soluble in the ethanol and was recovered by cooling the filtrate. The combined weight of the anilide was 32 g. (83%), m.p. 199–201°.

A sample was recrystallized twice from thiophene-free benzene, m.p. 201–202°.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2O_2$: C, 54.39; H, 3.26; N, 9.06.

Found: C, 54.52, H, 3.36; N, 8.91.

Ethyl m-chlorooxanilate. In an attempt to prepare this oxanilide by the method of Meyer and Seeliger (6), a mixture of 63.8 g. (0.5 mole) of *m*-chloroaniline and 365 g. (2.5 moles) of ethyl oxalate was heated under reflux for two hours. After cooling, the voluminous precipitate which had formed was collected and recrystallized from ethanol, 91 g. of white needles, m.p. 107–111°. Three recrystallizations from ethanol raised the melting point to 113–114°. The analysis of this compound corresponds to that of ethyl *m*-chlorooxanilate.

Anal. Calc'd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15.

Found: C, 52.76; H, 4.61; N, 6.26.

Preparation of m,m'-dichlorooxanilide imidochloride. Ten grams (0.032 mole) of *m,m'*-dichlorooxanilide was placed in 15 cc. of anhydrous benzene. After addition of 20 g. (0.096 mole) of phosphorus pentachloride, the mixture was heated under reflux on the steam-bath for two hours. On cooling, the mixture solidified to a yellow mass which was diluted with a small portion of petroleum ether. From the filtrate an additional amount of the imidochloride could be obtained by cooling. One recrystallization from low-boiling petroleum ether gave 10 g. (91%) of yellow needles, m.p. 112–116°. After two recrystallizations from high-boiling petroleum ether, it melted at 116–116.5°.

Anal. Calc'd for $C_{14}H_8Cl_4N_2$: C, 48.59; H, 2.33; N, 8.09; Cl, 40.99.

Found: C, 48.70; H, 2.42; N, 8.28; Cl, 40.26.

Reaction of the imidochloride with sodiomalonic ester. Powdered sodium was prepared by melting 3.1 g. (0.136 gram-atom) of sodium in 450 cc. of boiling toluene and stirring vigorously while cooling the mixture. To this mixture, maintained at 90°, 49.5 g. (0.372 mole) of malonic ester was slowly added. After addition the mixture was heated under reflux for thirty minutes. To this suspension of sodiomalonic ester, 24 g. (0.068 mole) of the imidochloride in 200 cc. of toluene was added slowly at 60–70°. The mixture was then heated for four hours at 85–90° and for one hour at 100–105°.

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[4] All melting points are corrected.

[5] The semimicro quantitative analyses were carried out by Miss Theta Spoor and Miss Lillian Hruda.

The reaction mixture was poured into water and filtered. The toluene layer was separated and the water layer extracted several times with ether. The combined ether-toluene extracts were dried, the solvent was removed at reduced pressure and the excess malonic ester by distillation at 2 mm. pressure. The oil which remained was cooled and covered with ethanol. A yellow solid slowly crystallized, yield 21 g., m.p. 120–165°.

The yellow solid was boiled with ethanol and filtered while hot. The alcohol-insoluble material was recrystallized twice from benzene, giving compound VI, m.p. 191–192°.

Anal. Calc'd for $C_{19}H_{14}Cl_2N_2O_4$: C, 56.32; H, 3.48; N, 6.92.
Found: C, 56.66; H, 3.78; N, 6.81.

The alcohol filtrate, in the refrigerator for several days, deposited 7 g. of compound V, m.p. 135–136°. One recrystallization from ethanol raised the melting point to 136–137°.

Anal. Calc'd for $C_{28}H_{30}Cl_2N_2O_8$: C, 56.66; H, 5.10; N, 4.72.
Found: C, 56.87; H, 5.00; N, 4.66.

Cyclization of compound V. 1. In diphenyl ether. Five grams of compound V was boiled under reflux for one hour in 50 cc. of diphenyl ether. The mixture was cooled and diluted with 50 cc. of high-boiling petroleum ether. By filtration, 4 g. of a grey solid was obtained. The material was boiled with glacial acetic acid and filtered. From the cooled filtrate 3.7 g. of white solid separated, m.p. 278–295° dec. Two recrystallizations from glacial acetic gave the constant melting point 295–296° dec. The analysis corresponds to that of compound VII.

Anal. Calc'd for $C_{22}H_{12}Cl_2N_2O_6$: C, 58.03; H, 2.66; N, 6.15; Cl, 15.58.
Found: C, 57.88; H, 2 91; N, 5.90; Cl, 15.38.

2. By use of phosphorus oxychloride. Two grams of compound V was heated under reflux with 25 cc. of phosphorus oxychloride for one hour. The cooled reaction mixture was poured onto cracked ice and allowed to stand overnight. The solid material (1 g.) had m.p. 189–190°. One recrystallization from benzene gave yellow needles, m p. 191–192°. A mixed melting point with compound VI showed no depression.

3. In concentrated sulfuric acid Two grams of compound V was mixed with 15 cc. of concentrated sulfuric acid and was allowed to stand at room temperature. From time to time an aliquot portion was removed and diluted with water. After a period of two weeks no reaction had taken place, since starting material was recovered. After a period of two months the entire mixture was diluted with water. A grey solid separated, and was recrystallized from hot water as fine white needles, m.p. 310–330° dec. The analysis corresponds to 2-amino-4-chlorobenzenesulfonic acid.

Anal. Calc'd for $C_6H_6ClNO_3S_3$: C, 34 71; H, 2.91; N, 6.75; Cl, 17.08
Found: C, 34.84; H, 3 07; N, 6 76; Cl, 17.08.

Approximately 50 mg. of the sulfonic acid was placed in 5 cc. of water and bromine water was added By filtration 60 mg. of 2,4,6-tribromo-3-chloraniline, m.p. 124–125°, was isolated (7). A mixed melting point with an authentic sample prepared from *m*-chloroaniline showed no depression.

Hydrolysis of compound VI. Five grams (0.0123 mole) of the material was boiled gently for one hour with 50 cc. of water containing 1.99 g. (0.0492 mole) of sodium hydroxide The cooled reaction mixture was extracted with ether and the ether layer was dried over potassium hydroxide. After removing the ether, the remaining oil was boiled for five minutes with 2 cc. of acetic anhydride. The reaction mixture was poured on ice and white crystals were obtained, m.p. 70–72°. A mixture with an authentic sample of *m*-chloroacetanilide melted at 71–72°.

The alkaline water layer above was acidified with hydrochloric acid, and three grams of a pale brown solid (IX) was isolated, m.p 120–122°. The material was insoluble in hot water, ethanol, and glacial acetic acid. It was very soluble in cold acetone and pyridine but could not be precipitated from either of the latter solvents by dilution.

A sample for analysis was prepared by washing the material with hot water and alcohol. The analysis corresponds to that of a hemihydrate of oxaloacetic acid *m*-chloranilide (IX). The melting point agrees with that (m.p. 122–123°) reported by Surrey and Cutler (3) for a compound assigned this structure.

Anal. Calc'd for $C_{10}H_8ClNO_4$ $0.5H_2O$: C, 47.92; H, 3.62; N, 5.59.
Found: C, 48.04; H, 3.91; N, 5.82.

Cyclization of compound VI. Two grams of the imide was heated under reflux for ten minutes with 20 cc. of diphenyl ether. The material dissolved within a few minutes and after ten minutes the cyclized product had separated. The mixture was cooled and diluted with an equal volume of high-boiling petroleum ether, giving 1.5 g. of a yellow solid which melted above 350°. A sample for analysis was recrystallized twice from hot pyridine. The analysis corresponds to that of compound X.

Anal. Calc'd for $C_{17}H_8Cl_2N_2O_3$: C, 56.85; H, 2.26; N, 7.80; Cl, 19.74.
Found: C, 56.71; H, 2.68; N, 7.99; Cl, 19.60.

Hydrolysis of compound VII. Two grams of the compound, m.p. 295–296°, was heated in 15 cc. of 10% sodium hydroxide solution. After five minutes the solid had dissolved and an orange color had developed. The mixture was heated under reflux for one hour; the odor of *m*-chloroaniline was evident although the compound was not isolated from the mixture.

The solution was acidified with hydrochloric acid and a purple solid separated as considerable carbon dioxide was evolved; 0.8 g., m.p. 95–100°. This product could not be purified and was not characterized. The filtrate, on standing overnight, deposited crystalline rosettes, m.p. 290–300°. One recrystallization from water raised the melting point to 306–309°. The analysis corresponds to that of compound VIII.

Anal. Calc'd for $C_{12}H_8ClNO$: C, 54.05; H, 3.02; N, 5.25; Cl, 13.30.
Found: C, 53.97; H, 3.09; N, 5.78; Cl, 13.20.

This compound failed to give iodoform when treated with sodium hypoiodite.

Preparation of ethyl m-chloromalonanilide. A mixture of 64 g. (0.4 mole) of malonic ester and 25.5 g. (0.2 mole) of *m*-chloroaniline was heated in an oil-bath maintained at 165–175° until 9 g. (0.2 mole) of ethanol had distilled. The excess malonic ester was removed by distillation at 2 mm. pressure. The residue was dissolved in 100 cc. of ethanol and cooled. Ten grams of *m*,*m'*-dichloromalonanilide separated, m.p. 160–162°. Recrystallization from ethanol gave white plates, m.p. 165–166°.

Anal. Calc'd for $C_{15}H_{11}Cl_2N_2O_2$: C, 55.91; H, 3.44; N, 8.70.
Found: C, 55.78; H, 3.65; N, 9.10.

The melting point has been reported as 175–176° (8).

The filtrate, after removing the dianilide, was diluted with a large volume of water. An oil separated which slowly solidified on cooling. Thirty-two grams (66.7%) of ethyl *m*-chloromalonanilide, m.p. 70–76°, was obtained. Recrystallization from 70% ethanol gave fine white plates, m.p. 75–76°.

Anal. Calc'd for $C_{11}H_{12}ClNO_3$: C, 54.66; H, 5.01; N, 5.80.
Found: C, 54.76; H, 4.88; N, 5.98.

Attempted cyclization of ethyl m-chloromalonanilide. According to Mayer and Heimann (4), half anilides of malonic ester cyclize to form 4-ethoxycarbostyrils when heated at 250°. Accordingly, 5.0 g. (0.028 mole) of crude ethyl *m*-chloroanilide (m.p. 70–76°) was added slowly to a flask maintained at 250°. After addition was complete the flask was heated for 25 minutes at 250°, and the contents dissolved in hot ethanol and boiled with Darco. Filtration followed by cooling failed to precipitate any solid. Dilution of the filtrate with 10% sodium carbonate precipitated 3.7 g. of a brown solid. Recrystallization from ethanol gave a white product, m.p. 161–165°. A mixture with an authentic sample of *m*,*m'*-dichloromalonanilide melted at 165°.

Preparation of p,p'-dinitrooxanilide. A mixture of 14.6 g. (0.1 mole) of ethyl oxalate and 27.6 g. (0.2 mole) of *p*-nitroaniline was melted and approximately 0.5 g. of metallic sodium in small slices was added (5). After a few minutes of stirring, the mixture solidified. The solid material was washed several times with dilute hydrochloric acid and then alcohol. Recrystallization from aniline gave 25 g. (76%) of *p*,*p'*-dinitrooxanilide, m.p. 359° (corr.). The recorded melting point is 260° (9).

Anal. Calc'd for $C_{14}H_{10}N_4O_6$: C, 50.91; H, 3.05.
Found: C, 51.01; H, 3.20.

Reaction of phosphorus pentachloride with p,p'-dinitrooxanilide. A mixture of 12.3 g. (0.037 mole) of *p,p'*-dinitrooxanilide and 15.4 g. (0.074 mole) of phosphorus pentachloride was heated under reflux for two and one-half hours at 180–200°. The reaction mixture, which had turned brown, was cooled and 150 cc. of anhydrous benzene added, yield, 9 g. of solid material. It was boiled with 250 cc. of dioxane and filtered while hot. Two grams of insoluble *p,p'*-dinitrooxanilide was collected, m.p. 357°. The filtrate, after standing overnight, had deposited 3.5 g. of a brown solid. Dilution of the dioxane solution with water gave an additional 2.7 g. of this material. It was recrystallized from dioxane until a constant melting point, 239–241°, was obtained. The compound had the composition of the imidochloride of *p,p'*-dinitrooxanilide.

Anal. Calc'd for $C_{14}H_8Cl_2N_4O_4$: C, 45.80; H, 2.20; N, 15.26.
Found: C, 45.91; H, 2.25; N, 15.38.

In another similar experiment starting with 24.6 g. (0.074 mole) of the anilide and 35 g. (0.120 mole) of phosphorus pentachloride, 18.6 g. (68%) of the imidochloride was obtained.

Attempted preparations of p,p'-dinitrodithiooxanilide. 1. By reaction of phosphorus pentasulfide with p,p'-dinitrooxanilide. Following the method of Reissert (10), 20 g. (0.067 mole) of *p,p'*-dinitrooxanilide was refluxed in 350 cc. of xylene for one hour. To the boiling mixture, 10 g. of phosphorus pentasulfide was added, followed by refluxing for seven hours. The solution was filtered and the filtrate was freed from xylene by steam-distillation. The residue was allowed to stand in 5% alkali overnight. Carbonation precipitated a small amount of red material which could not be crystallized from alcohol. The compound was soluble in chloroform, petroleum ether, and glacial acetic acid. When dissolved in glacial acetic acid it could be precipitated by dilution with water. Reprecipitation from acetic acid three times gave a dark red amorphous solid which sintered at 180° and melted at 204°. Analysis by the sodium fusion method indicated the presence of both nitrogen and sulfur. The carbon and hydrogen analysis did not correspond to those required for the dinitrodithiooxanilide but the values obtained corresponded approximately to the composition of *p,p'*-diaminodithiooxanilide, which might have been formed by the reduction of the dinitrodithiooxanilide.

Anal. Calc'd for $C_{14}H_{14}N_4S_2$: C, 55 63; H, 4.66.
Found: C, 54 48; H, 5 46.

The reaction was repeated using the same amounts as above but substituting nitrobenzene for the xylene. The residue from the steam-distillation of the nitrobenzene consisted of tarry material which was insoluble in sodium hydroxide.

2. By reaction of potassium hydrosulfide with the imidochloride of p,p'-dinitrooxanilide. Two grams of potassium hydroxide was dissolved in 25 cc. of hot absolute alcohol and saturated with hydrogen sulfide To the solution of potassium hydrosulfide, 2 g. (0.0054 mole) of the purified imidochloride was added and the mixture refluxed for forty minutes. The dark red mixture was added to 100 cc. of 5% sodium hydroxide and allowed to stand overnight. Filtration followed by carbonation precipitated a red solid, m.p. 190–200°. All attempts to recrystallize the material failed. A mixture with the compound obtained above melted 189–205°. No further attempts were made to identify the compound.

3. By reaction of p-nitroaniline with carbon disulfide in the presence of stannous oxide. The procedure of Cecchetti and Sarti (11) was followed. To a mixture of 6.07 g. (0.044 mole) of *p*-nitroaniline in 150 cc. of absolute ethanol, 4.88 g. (0.15 mole) of carbon disulfide was added. Three grams (0.022 mole) of stannous oxide, freshly prepared from stannous chloride, was added and the mixture stirred at room temperature for twenty-four hours. Filtration of the mixture resulted in the complete recovery of the stannous oxide, indicating that no reaction had taken place. Evaporation of the filtrate gave 5.95 g. of *p*-nitroaniline.

Preparation of p-dimethylamino-p'-nitrooxanilide. A mixture of 29.2 g. (0.2 mole) of ethyl oxalate and 27.6 g. (0.2 mole) of *p*-nitroaniline was refluxed for five hours. The mixture was washed once with 95% alcohol and filtered. The ethyl *p*-nitrooxanilate (22 g., 24%) was recrystallized from alcohol, m.p. 170–171° [lit. (12) ,171°].

Following the directions given by Suida (13), 10 g. (0.042 mole) of ethyl *p*-nitrooxanilate and 5.7 g. (0.042 mole) of *p*-dimethylaminoaniline were rapidly heated to 180° and maintained at this temperature for thirty minutes. The solid mass was diluted with an alcohol-water mixture and filtered. The material was dried and ground to a powder in a mortar. The red powder was washed with alcohol and dried, giving 9.2 g. (67%) of *p*-dimethylamino-*p'*-nitrooxanilide, m.p. 292–295°. Recrystallization three times from redistilled aniline gave red needles, m.p. 309–309.5°.

Anal. Calc'd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.07.
Found: C, 58.21; H, 5.14; N, 17.22.

Reaction of phosphorus pentachloride with p-dimethylamino-p'-nitrooxanilide. A mixture of 11.7 g. (0.056 mole) of phosphorus pentachloride and 9 g. (0.027 mole) of the anilide was heated at 140° for thirty minutes. The reaction mixture was extracted with benzene and then hot dioxane. The benzene extract, when evaporated, gave a small amount of yellow-brown material. The material, which melted at 170–200°, could not be recrystallized from any solvent.

The reaction was repeated using a mixture of 5.8 g. (0.028 mole) of phosphorus pentachloride and 4.5 g. (0.014 mole) of the anilide which was refluxed for two hours in 100 cc. of benzene. The reaction mixture was diluted with water and the benzene extracts were evaporated to dryness. Again about 0.5 g. of an intractable yellow solid, m.p. 160–190° was isolated.

Attempted preparation of p-dimethylamino-p'-nitrodithiooxanilide. Ten grams (0.03 mole) of *p*-dimethylamino-*p'*-nitrooxanilide and five grams of phosphorus pentasulfide were refluxed in 200 cc. of xylene for one hour. The hot xylene mixture was filtered and the xylene evaporated by a stream of air. The residue was extracted with ether and the ether evaporated. The dark red material which remained was insoluble in alkali.

In another similar experiment after evaporation of the xylene, the residue was allowed to stand with 5% alkali for twenty-four hours. Filtration and saturation of the filtrate with carbon dioxide failed to precipitate any solid material.

SUMMARY

The preparation of several new oxanilide derivatives has been described, as well as some attempts to convert them into quinolines and into dithio derivatives.

URBANA, ILL.

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[Contribution from the Department of Chemistry of Columbia University]

PROOF OF THE POSITION OF THE ACETYL GROUP IN CERTAIN 9-ACETYL-3-SUBSTITUTED RETENES. DIALKYLAMINO CARBINOLS FROM 9-ACETYL-3-CHLORORETENE[1]

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In a previous communication, the synthesis of a number of representative retene-3-dialkylamino carbinols has been described (1). These substances showed a low order of antimalarial activity when tested against avian malaria (2). Since phenanthrene-9-amino carbinols, particularly certain of those carrying halogen substituents, with the amino carbinol group in the 9-position displayed a relatively high order of activity (3), it appeared to be of interest to explore analogous retene derivatives, in view of the potential availability of retene in practically unlimited amounts. Furthermore, a nuclear substituent can be readily introduced into the 3-position of retene through the easily prepared 3-acetyl retene, and with such a substituent present, a new acetyl group would presumably enter either the 9- or 10-positions, thus opening up a series of drugs closely analogous to the more active phenanthrene types. At the same time, information would be obtained as to the influence of the position of the amino carbinol side chain on antimalarial activity in the retene series.

Based on experience in the phenanthrene series (3), chlorine was selected as the substituent to be introduced in the 3-position of retene. Several references to the direct chlorination of retene appear in the literature, in most of which the isolation of no well defined product is reported. Karrman (4) has very recently reported the isolation of 9- (or 10-)-chlororetene in very small yield from the reaction products of the chlorination of retene according to Komppa and Wahlforss (5). In any event, little likelihood of success seemed probable if the introduction of the chlorine was attempted by direct chlorination. Therefore the chlorine atom was introduced by the series of reactions I–V proceeding from 3-acetylretene (I) in which the position of the acetyl group has been demonstrated by Campbell and Todd (6).

3-Acetaminoretene (III) has been prepared previously (7) in low yield by Beckmann rearrangement of the oxime (II). Application of the method of Bachmann and Boatner (8) to the rearrangement of the oxime (II) has resulted in greatly improved yields of III. In this connection it is interesting to note that only the *trans*-form of the oxime (II) was encountered in the present work, as evidenced by complete rearrangement of II. Bachmann and Boatner (8) obtained mixtures of *cis*- and *trans*-oximes in the formation of the four acetylphenanthrenes, namely, the 1-, 2-, 3-, and 9-derivatives, studied by them. Replacement of the amino group by halogen in phenanthrene derivatives has

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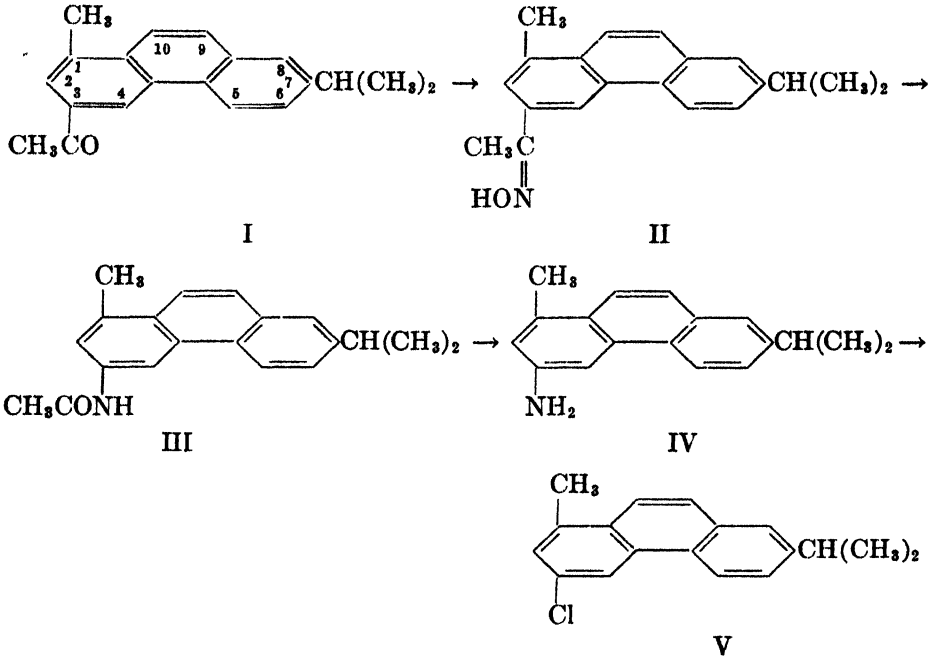
[1] The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.



I II III IV V

been reported by Bachmann and Boatner (9) and very recently by Schultz and co-workers (10). The former workers isolated the double salt of 1-,2-, and 3-phenanthrene diazonium derivatives with mercuric chloride, followed by decomposition of the latter in the presence of the appropriate potassium halide. The latter workers dealt exclusively with the 9-phenanthrene halides. By employing a modification of the usual Sandmeyer reaction it has now been possible to prepare 3-chlororetene (V) in yields substantially higher than those reported heretofore for analogous phenanthrene compounds.[2] Thus a monochlororetene of definite structure has been prepared for the first time.

3-Chlororetene (V) readily underwent the Friedel-Crafts reaction with acetic anhydride to yield 9-acetyl-3-chlororetene the structure of which was demonstrated as follows. Campbell, Soffer, and Steadman (11) report a similar reaction with 3-methoxy- or 3-acetoxy-retene, and assign either the 9- or 10-position to the acetyl group introduced, with the 9-position favored by analogy based on observations of Fieser and Young (12), in which a certain amount of steric hindrance relative to the 10-position is noted in certain coupling reactions of 1-alkylphenanthrenes. On the assumption that the chlorine in V exerts the same orienting influence, or lack of it, as do the methoxyl and acetoxyl groups, the new acetyl group in (VI) may accordingly be assigned either the 9- or 10-positions. This assumption was proved by the formation of the same 3-chlororetenequinone (VII) on oxidation of either V or VI. The 10-position as the location of the

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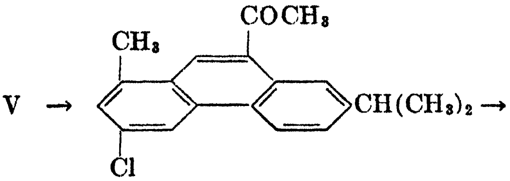
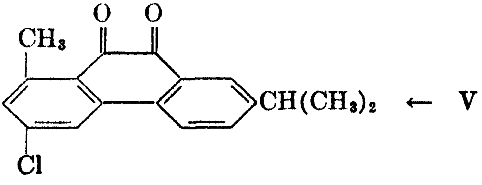
[2] Equally satisfactory results have been obtained in the preparation of 2- and 3-chlorophenanthrene by this method. Details of these experiments will appear elsewhere.

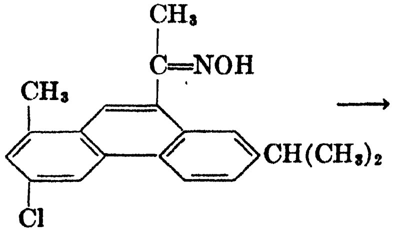


VI

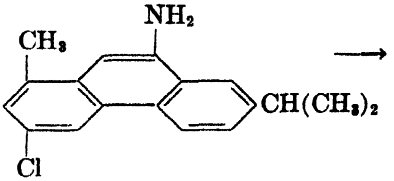


VII

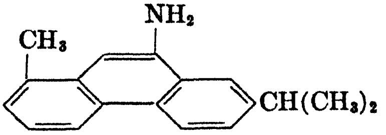
acetyl group in VI was definitely eliminated by the reaction shown in formulas VIII–XI.



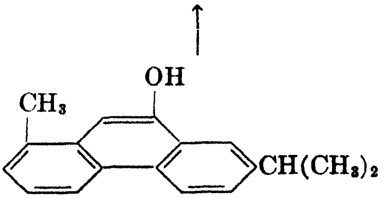
VIII



IX



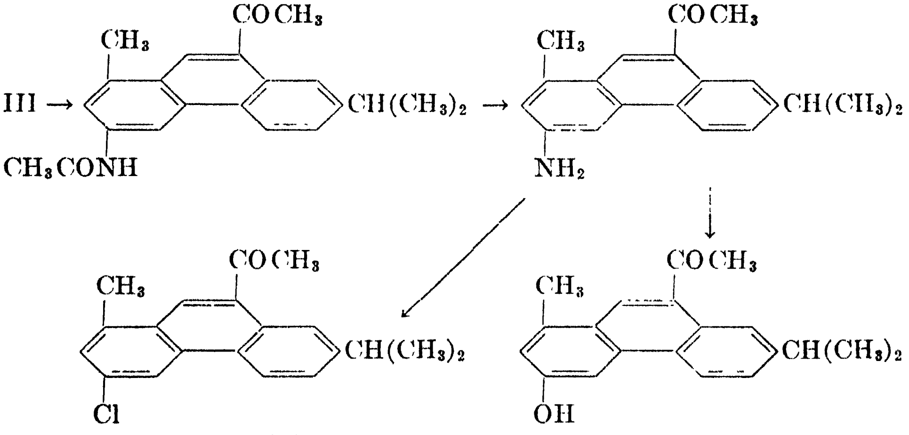
X



XI

On Beckmann rearrangement of the oxime of VI (VIII), 3-chloro-9-acetaminoretene was obtained, which on hydrolysis readily yielded 3-chloro-9-aminoretene (IX). Catalytic removal of the chlorine in IX gave 9-aminoretene (X). X was also prepared by the Bucherer reaction from 9-retenol (XI) which has been synthesized by Fieser and Young (12). Samples of X prepared by either route were identical, as were the hydrochlorides and acetyl derivatives of the substance prepared in the two ways. Since the structure of 9-methoxyretene has been rigidly established by its total synthesis by Keimatsu, Ishiguro, and Sumi (13), it follows that the structure assigned to 9-retenol by Fieser and Young on the basis of steric considerations is correct, and further, that the acetyl group in VI is in the 9-position. In an alternate scheme for carrying out the above correlation, conversion of IX to 3-chloro-9-hydroxyretene over the diazonium reaction was attempted. Difficulty was encountered in carrying out the diazotization, possibly due to the extreme insolubility of salts of IX in water. In one experiment 3-chlororetenequinone was isolated from the reaction products. Likewise an attempt was made to reduce 3-chlororetenequinone to 3-chloro-9-acetoxyretene by the procedure of Fieser and Young (12) for the similar reduction of retenequinone. Only 3-chloro-9,10-diacetoxyretene could be isolated from the reaction products.

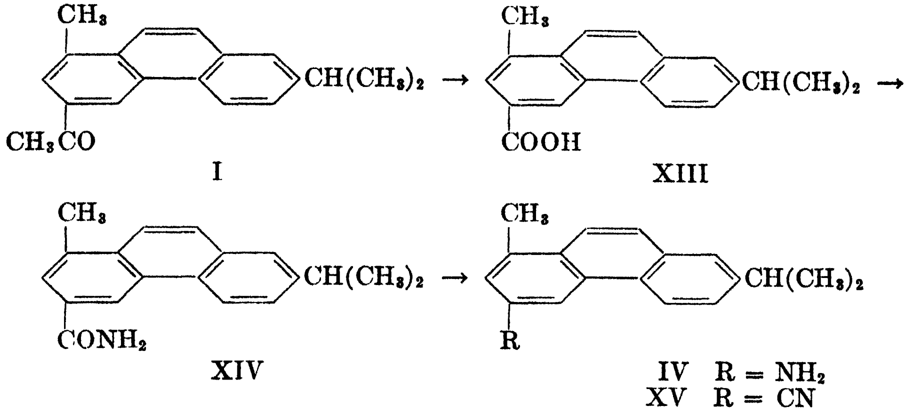
Finally, in order to furnish confirmatory evidence in support of Campbell, Soffer, and Steadman's view that 3-methoxy- and 3-acetoxy-retene acylate probably in the 9-position in the Freidel-Crafts reaction, 3-acetaminoretene (III) was subjected to acetylation with acetic anhydride. The product, 3-acetamino-9-acetylretene in turn was hydrolyzed to 3-amino-9-acetylretene from which 3-chloro-9-acetylretene (VI) and 9-acetyl-3-retenol (XII) were prepared by the diazonium reaction.



VI XII

The sample of VI thus prepared was identical with VI prepared by acetylation of 3-chlororetene, the structure of which has been demonstrated above. Likewise the sample of XII was identical with a sample of XII prepared by the method of Campbell, Soffer, and Steadman. Therefore the fact that 3-acetoxy- and 3-methoxy-retene acetylate in the 9-position in the Friedel-Crafts reaction has been rigidly proved. The generalization therefore appears warranted, that if an *ortho, para* orienting group is present in the 3-position in retene, introduction of an acyl group by the Friedel-Crafts reaction takes place in the 9-position.

Before arriving at the above satisfactory synthesis for 3-aminoretene, preparation of this was undertaken by the reactions shown below.



I

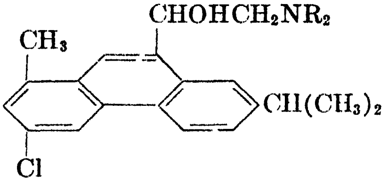
XIII

XIV

IV R = NH_2
XV R = CN

Retene-3-carboxylic acid (XIII) (5, 14) and its amide (XIV) (5) have been prepared by methods more convenient than those heretofore described. Attempted conversion of XIV to the amine IV, failed despite the use of a variety of conditions. XIV was however converted smoothly to the nitrile, (XV) which in turn failed to undergo the Friedel-Crafts reaction.

The synthesis of representative dialkylamino carbinols (XVI) from VI proceeded readily using the general methods employed in the preparation of the retene-3-amino carbinols (1). Of these the di-*n*-amyl derivative (XVI, R = *n*-C_5H_{11}) was found to have a quinacrine equivalent of 4 when tested against *gallinaceum* malaria (15). A higher avian activity than that of the retene-3-amino carbinols has thus been achieved.



XVI

EXPERIMENTAL[3]

3-Acetaminoretene (*III*). This has been prepared in 35% yield by Cassaday and Bogert (7). The method of Bachmann and Boatner (8) for the synthesis of 3-aminophenanthrene here used gives much higher yields. To a stirred suspension of 136 g. of the oxime (16) of 3-acetylretene (1) in 1500 ml. of dry benzene cooled in an ice-bath was added during two minutes 107 g. of phosphorus pentachloride. The mixture was left in the ice-bath for fifteen minutes and then allowed to stand at room temperature for three hours, during which the solid dissolved practically completely. On pouring into 1500 ml. of ice and water and stirring for two hours the acetamino compound separated as a very finely divided yellow solid. After filtering and washing with dilute alcohol, 122 g. (90%) of material melting at 238.5–240.5° was obtained. A sample recrystallized from a large volume of alcohol melted at 241–241.5°. Cassaday and Bogert (7) report 240–241°.

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[3] All melting points are corrected except where otherwise stated. Microanalyses by Miss Lois May of these laboratories.

3-Aminoretene (IV). A mixture of 121 g. of crude 3-acetaminoretene, 1750 ml. of alcohol and 180 ml. of hydrochloric acid (sp. gr. 1.19) was heated under reflux for six hours, during which the solid dissolved. This was treated with carbon, and excess ammonia was carefully added to the hot solution. The aminoretene hydrochloride crystallizes if its solution is allowed to cool. The ammoniacal solution was poured into 2.5 l. of ice-water whereupon 93 g. (90%) of crude 3-aminoretene separated. This was used directly for the next reaction. Cassaday and Bogert (7) prepared 3-aminoretene by alkaline hydrolysis of the acetamino compound.

3-Chlororetene (V). For the Sandmeyer reaction on 3-aminoretene, either the free base or the hydrochloride may be used, but use of the latter has been found to result in purer 3-chlororetene. A warm solution of 93 g. of 3-aminoretene in 1500 ml. of dry ether was carefully cooled in an ice-bath so as to maintain a supersaturated solution. Dry hydrogen chloride was then carefully passed over the solution until precipitation of the hydrochloride was complete. The yield of material melting with decomposition at 269–275° was theoretical. Cassaday and Bogert (7) report the melting point as 267–273° dec.

A solution of 150 g. of 3-aminoretene hydrochloride in 2500 ml. of glacial acetic acid and 1050 ml. of hydrochloric acid (sp.gr. 1.19) was cooled to −3° in a 5-liter three-necked flask equipped with an efficient mechanical stirrer, thermometer, dropping-funnel, and gas outlet tube. To this was added a solution of 105 g. of sodium nitrite in 195 ml. of water with stirring during one hour at such a rate that the inside temperature did not exceed 0°. Strong external cooling was necessary. The red-orange solution was stirred at 0° for an additional three hours. A solution of 90 g. of urea in 250 ml. of water was added during one hour while the inside temperature was kept below 3°, and the solution was stirred for another thirty minutes at 3°.

Meanwhile a solution of cuprous chloride was prepared by adding a hot solution of 113 g. of sodium bisulfite and 78 g. of sodium hydroxide in 900 ml. of water to a boiling solution of 525 g. of copper sulfate pentahydrate and 143 g. of sodium chloride in 1800 ml. of water. After cooling, the cuprous chloride was filtered and washed with water. It was then dissolved in 1050 ml. of hydrochloric acid (sp.gr. 1.19) and cooled to −5°. To this was added the cold diazonium solution with stirring during one minute. Very little heat was evolved. The mixture was left overnight at room temperature, then stirred for five hours and the tan solid (143 g.) was filtered and washed thoroughly with water. This was dissolved in 1200 ml. of ether and treated with decolorizing carbon. The light amber solution was concentrated to a quarter of its volume and 1200 ml. of methanol was added. Crystallization of the chlororetene as yellow-tan cubes was rapid. After recrystallization from the same solvents the material melted at 108–109°. All the mother liquors were combined, evaporated and the residue distilled at 0.01 mm., collecting the fraction boiling at 155–165°. This was recrystallized as before, yielding further pure material. The total yield was 104 g. (74%).

Anal. Calc'd for $C_{18}H_{17}Cl$: C, 80.4; H, 6.4.
Found: C, 80.5; H, 6.4.

3-Chloro-9-acetylretene (VI). To a solution of 91 g. of 3-chlororetene in 900 ml. of dry nitrobenzene contained in a flask equipped with an efficient mechanical stirrer, thermometer, aluminum chloride addition tube, and a gas outlet tube was added 40 ml. of acetic anhydride. After cooling to 3°, at which temperature the nitrobenzene began to freeze, 113 g. of anhydrous aluminum chloride was added with stirring during one and one-half hours and the inside temperature was lowered to −1°. The mixture was protected from moisture and stirred for an additional two hours at −1° and then allowed to stand at room temperature overnight. After stirring for three hours at room temperature, it was cooled to 0°, stirred for another hour and the solid was filtered off The complex was washed at 0° with petroleum ether until free of nitrobenzene. The light orange solid was broken up and added to a stirred mixture of 600 g. of ice and 200 ml. of hydrochloric acid (sp.gr. 1.19). After thirty minutes the cream colored precipitate was extracted with several portions of chloroform. The combined extracts were washed with sodium bicarbonate solution, dried, and the solvent removed, leaving an amber oil which solidified rapidly. This was dissolved in 225 ml. of hot ether and on cooling 37 g. of long white needles separated. The mother liquors were treated with carbon, evaporated and the residue was crystallized from alcohol using seeds from the first crop, and a second crop of material was obtained. After recrystallization from alcohol the substance melted at 114°. The yield was 48 g. (46%).

Anal. Calc'd for $C_{20}H_{19}ClO$: C, 77.3; H, 6.2.
Found: C, 77.3; H, 6.2.

3-Chloro-9-acetylretene oxime. When 3-chloro-9-acetylretene (7 g.) was refluxed with 4 g. of hydroxylamine hydrochloride in 100 ml. of alcohol for three hours and the solution evaporated to 55 ml. and cooled, 7 g. of oxime was obtained. One recrystallization from alcohol yielded a mixture of the *cis-* and *trans*-oximes as non-homogeneous needles which melted at 159.5–162.5°. Further separation of the isomers was not attempted.

3-Chlororetenequinone (VII). A. From 3-chlororetene. The general method of Komppa and Wahlforss (5) was used. To a warm solution of 1.1 g. of 3-chlororetene in 3.5 ml. of glacial acetic acid was added a solution of 1.9 g. of chromic acid in 10 ml. of acetic acid during five minutes. After refluxing for ten minutes, the mixture was cooled and the solid which separated was filtered off and washed with water. Two recrystallizations from 150 ml. of methanol gave 0.35 g. of yellow-orange needles melting at 210–210.5°.

Anal. Calc'd for $C_{18}H_{15}ClO_2$: C, 72.3; H, 5.1.
Found: C, 72.1; H, 5.1.

3-Chlororetophenazine. To a suspension of the above quinone (0.1 g.) in 4 ml. of hot glacial acetic acid was added a solution of 0.13 g. of *o*-phenylenediamine dihydrochloride and 0.1 g. of fused sodium acetate in the minimum amount of 70% alcohol. After refluxing for ten minutes the mixture was cooled and the precipitate was recrystallized from glacial acetic acid yielding the phenazine as pale yellow needles melting at 179.5–180.5°.

Anal. Calc'd for $C_{24}H_{19}ClN_2$: C, 77.8; H, 5.2.
Found: C, 77.7; H, 5.1.

B. From 3-chloro-9-acetylretene. The general method of Fieser and Young (12) was used. To a solution of 0.5 g. of 3-chloro-9-acetylretene in 1.4 ml. of warm glacial acetic acid was added a solution of 0.75 g. of chromic acid in 4 ml. of glacial acetic acid during five minutes. The mixture was refluxed for ten minutes, hot water was added, and, after cooling, the solid (0.24 g.) was filtered off and dissolved in hot alcohol, and 10 ml. of a hot saturated solution of sodium bisulfite was added. Sufficient water was added to dissolve precipitated sodium bisulfite. The solution was filtered and acidified with hydrochloric acid. On warming, 3-chlororetenequinone crystallized. After recrystallization from methanol, it melted at 210–210.5° and did not depress the melting point of 3-chlororetenequinone prepared from 3-chlororetene.

The phenazine prepared from the above quinone melted at 176.5–177.5° and did not depress the melting point of the phenazine prepared previously.

3-Chloro-9,10-diacetoxyretene. To a suspension of 0.2 g. of 3-chlororetene quinone in 1.4 ml. of hot glacial acetic acid, 0.08 g. of zinc dust was slowly added and the mixture was boiled for thirty minutes. The initial orange mixture became very dark and then began to lighten in color. At fifteen-minute intervals four additional 0.06-g. portions of zinc dust were added to the boiling solution. A solution of 0.3 g. of fused sodium acetate in 4.5 ml. of acetic anhydride was added to the mixture which was then refluxed for one hour. After cooling, the solution was decanted from unreacted zinc into 40 ml. of cold water. After boiling to decompose the acetic anhydride, a mixture of 3-chloro-9,10-diacetoxyretene and 3-chloro-9-acetoxyretene separated. After several recrystallizations from ether, the diacetoxy compound formed fluffy needles which melted at 212–213°.

Anal. Calc'd for $C_{22}H_{21}ClO_4$: C, 68.7; H, 5.5.
Found: C, 68.8; H, 5.5.

The ether mother liquors contained 3-chloro-9-acetoxyretene by analogy with the work of Fieser and Young (12) on 9-acetoxyretene, whose method was followed closely. This point was not investigated.

9-Aminoretene (X). 9-Acetoxyretene was prepared by reduction of retenequinone according to Fieser and Young (12), except that the crude product was crystallized directly from a large volume of methanol, rather than subjecting it to distillation. Hydrolysis of the acetoxyl group gave 9-retenol (12). A mixture of 5.5 g. of 9-retenol, 27.5 g. of a well stirred suspension of ammonium sulfite, prepared by passing sulfur dioxide into 19.5 ml. of ammonium hydroxide cooled in an ice-bath until the weight increased 8 g., and 27.5 ml. of ammonium hydroxide (d. 0.9) was heated in a sealed tube for twenty-five hours at 140°. The cooled contents of the tube were extracted with ether, and the extract was washed with 5% sodium hydroxide solution, then with water, and dried over magnesium sulfate. Dry hydrogen chloride was carefully passed over the surface of the solution until no more precipitate was formed, yielding 3.5 g. (56%) of 9-aminoretene hydrochloride melting at 245–248°. The mother liquors were evaporated to dryness and the residue was recrystallized. from xylene (charcoal) yielding 2.3 g. (42%) of recovered 9-retenol melting at 179-180.

Decomposition of the amine hydrochloride by shaking with ether and 5% sodium hydroxide gave the free amine, which formed clusters of fluffy needles, melting at 131.5–132.5°, after recrystallization from ether-petroleum ether.

Anal. Calc'd for $C_{18}H_{19}N$: C, 86.7; H, 7.7.
Found: C, 86.8; H, 7.5.

9-Acetaminoretene. The above amine (0.3 g.) was acetylated by refluxing with 6 ml. of acetic anhydride for ten minutes. After decomposition of the excess anhydride, the acetamino compound was recrystallized from ethyl acetate as white needles which melted at 210.5–211°.

Anal. Calc'd for $C_{20}H_{21}NO$: C, 82.4; H, 7.3.
Found: C, 82.2; H, 7.2.

3-Chloro-9-acetaminoretene. To a cooled suspension of 5.5 g. of crude 3-chloro-9-acetylretene oxime, prepared as above, in 90 ml. of dry benzene, 5.5 g. of phosphorus pentachloride was added. The mixture was boiled for fifteen minutes and the clear yellow solution was evaporated to about 45 ml. On pouring into 150 ml. of ice and water a finely divided solid separated. This was filtered off and washed thoroughly with water, yielding 4 g. of material melting at 233–235° with sintering at 220°. This probably contained some amide from the *cis*-oxime and was used directly in the next reaction.

Pure material was, however, obtained by acetylation of 3-chloro-9-aminoretene prepared as below. After recrystallization from ethyl acetate it formed silky white needles which melted at 242.5–243°.

Anal. Calc'd for $C_{20}H_{20}ClNO$: C, 73.8; H, 6.2.
Found: C, 73.9; H, 6.2.

3-Chloro-9-aminoretene (IX). A mixture of 4 g. of crude 3-chloro-9-acetaminoretene, 225 ml. of alcohol, and 10 ml. of hydrochloric acid (sp.gr. 1.19) was refluxed for five hours. To the hot solution 13 ml. of ammonium hydroxide (*d.* 0.9) was carefully added. The residue obtained on evaporation to dryness was thoroughly extracted with ether and the combined ether extracts decolorized with carbon. Dry hydrogen chloride was carefully passed over the surface of the solution, and 2.5 g. of amine hydrochloride separated as white needles. After one recrystallization from alcohol, the amine hydrochloride, melting at 239–242.5°, was dissolved in the minimum amount of hot alcohol, and hot water was added to the stirred solution until no more crystals separated. On cooling, a practially theoretical yield of the base separated. After recrystallization from ether it formed colorless small squares which melted at 158.5–159.5°.

Anal. Calc'd for $C_{18}H_{18}ClN$. C, 76.2; H, 6.4.
Found: C, 76.0; H, 6.3.

Reduction of 3-chloro-9-aminoretene. A suspension of 0.5 g. of palladium on calcium carbonate catalyst (17) containing 10 mg. of palladium, in 40 ml. of alcohol was shaken in a

Paal duck with hydrogen at atmospheric pressure until saturated. To this was added 0.1 g. of 3-chloro-9-aminoretene through an addition tube without opening the duck. After one and one-half hours, one equivalent of hydrogen had been absorbed and reduction ceased. The filtrate from the catalyst was evaporated to dryness yielding 9-aminoretene, which was isolated and purified as the hydrochloride. The melting points of the free amine, its hydrochloride, and the acetamino derivative agreed with those for the corresponding derivatives prepared as above from 9-retenol, and the melting points of mixtures of the three compounds prepared by the two methods were not depressed.

3-Acetamino-9-acetylretene. To a well stirred paste of 84 g. of 3-acetaminoretene in 800 ml. of dry carbon bisulfide and 54 ml. of acetic anhydride at room temperature, in a 3-liter flask equipped with an efficient stirrer, reflux condenser, inside thermometer, and an addition tube for addition of solids, 154 g. of anhydrous aluminum chloride was added over twenty minutes, during which the mixture warmed up to 40°. It was then refluxed for two hours. The condenser was set downward for distillation and a liter separatory funnel was connected to the flask. Water (1000 ml.) was added dropwise to the stirred solution, the heat of hydrolysis causing distillation of the solvent. The aqueous suspension was heated for an additional hour on the steam-bath, cooled, and filtered, yielding 75 g. of crude product. This was treated with charcoal in a large volume of acetone, yielding 3-acetamino-9-acetylretene as lustrous white needles melting at 265.5–266.5°. After working up the mother liquors, the total yield was 62 g. (65%).

Anal. Calc'd for $C_{22}H_{23}NO_2$: C, 79.3; H, 7.0.
Found: C, 79.3; H, 7.0.

3-Amino-9-acetylretene. The above acetamino compound (1.5 g.) was refluxed with 4 ml. of hydrochloric acid (sp.gr. 1.19) and 30 ml. of alcohol for five hours. After making the solution ammoniacal, it was worked up as in the previous case by evaporation to dryness and extraction of the residue with ether. Passage of dry hydrogen chloride over the ether solution of the base precipitated 1.2 g. of amine hydrochloride, which charred without melting at 216°. The hydrochloride was decomposed as in the preceding case by precipitation of its hot alcoholic solution with hot water. The amine formed pale yellow, long, thin needles which melted at 174.5–175.5°.

Anal. Calc'd for $C_{20}H_{21}NO$. C, 82.4; H, 7.3.
Found: C, 82.3; H, 7.2.

9-Acetyl-3 retenol (XII) A crude sample of 9-acetyl-3-retenol[4] prepared by acetylation of 3-acetoxyretene and hydrolysis of the product according to the method of Campbell, Soffer, and Steadman (11) was recrystallized from methanol; needles melting at 249.5–250.5°. Campbell, Soffer, and Steadman (11) report the melting point as 247–248° but did not analyze their sample.

Anal. Calc'd for $C_{20}H_{20}O_2$: C, 82.2; H, 6.9.
Found: C, 82.0; H, 6.9.

9-Acetyl-3-retenol from 3-amino-9-acetylretene. 9-Acetyl-3-aminoretene (50 mg.) was ground up with 3.7 ml. of 0.1 *N* hydrochloric acid To the ice-cold stirred suspension was added during thirty seconds a solution of 14 mg. of sodium nitrite in 1 ml. of water. After stirring for five minutes, the solution was filtered from a small amount of insoluble material and warmed on the steam-bath. When nitrogen evolution ceased, the mixture was cooled, and the pinkish flocculent crystals were recrystallized three times from methanol with one treatment with carbon. The phenol formed fluffy needles which melted at 249.5–250.5°, and the melting point was not depressed on admixture with an authentic sample of 9-acetyl-3-retenol.

Acetylation of the above phenol by refluxing with acetic anhydride for ten minutes yielded 3-acetoxy-9-acetylretene as white plates which melted at 169–170°. The mixed melting point with an authentic sample was not depressed. Campbell, Soffer, and Steadman (11) prepared what they considered either 9- or 10-acetyl-3-acetoxyretene by application of the Friedel-Crafts reaction to 3-acetoxyretene. The melting point reported by them is 169–170°.

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[4] Courtesy of Dr. Chester B. Kremer of these laboratories.

3-Chloro-9-acetylretene from 3-amino-9-acetylretene. To an ice-cold solution of diazotized 3-amino-9-acetylretene prepared from 50 mg. of the amine as above was added 1 ml. of an ice-cold cuprous chloride solution prepared as described under the synthesis of 3-chlororetene. After allowing the mixture to come to room temperature it was stirred for four hours. The solid material which separated was collected, dissolved in ether, and the filtered solution was evaporated, leaving a rapidly crystallizing oil. After two recrystallizations from alcohol, white needles melting at 113–114° were obtained. The mixed melting point with a sample prepared from 3-chlororetene as given above was not depressed.

Retene-3-carboxylic acid (XIII). A solution of sodium hypochlorite prepared by passing 58 g. of chlorine into a solution of 80 g. of sodium hydroxide in 110 ml. of water and 450 g. of ice, was placed in a 3-liter flask equipped with a stirrer and thermometer and mounted on a steam-bath, in such a manner than an ice-bath could be quickly substituted, and warmed to 60°. To this stirred solution was added 50 g. of 3-acetylretene (1) and the mixture was warmed to 65°. No apparent reaction took place. The steam-bath was removed and 250 ml. of dioxane was added. After a few seconds the temperature began to rise rapidly, the ice-bath was quickly applied and the temperature was held at 70–75°. The solid dissolved rapidly and the reaction was over in five minutes. The stirred mixture was allowed to cool to room temperature, during which the sodium salt of the acid precipitated. Excess chlorine was removed by addition of sodium bisulfite (5–10 g.) and the mixture was acidified with hydrochloric acid. On cooling, 51 g. (100%) of retene-3-carboxylic acid separated. The crude acid melted at 231–234°. Adelson and Bogert (14a), who prepared the acid from 3-acetylretene using sodium hypoiodite, report the melting point 238–238.5°.

Retene-3-carboxylic acid amide (XIV). To a suspension of 52 g. of the above acid in 125 ml. of ether was added 54.5 ml. of pure thionyl chloride. No violent reaction occurred. After standing for twenty-four hours protected from moisture, the mixture was concentrated to dryness under reduced pressure at room temperature. To the tan crystalline residue, 350 ml. of benzene was added followed by 250 g. of ice and 100 ml. of ammonium hydroxide (*d.* 0.9) slowly and with stirring. The white flocculent amide weighed 52 g. (100%) and melted at 229–232°. Komppa and Wahlforss (5) report the melting point of the amide as 224–226° (uncorr.).

3-Cyanoretene (XV). An intimately ground mixture of 2 g. of the above amide and 3 g. of phosphorus pentachloride was heated on the steam-bath with protection from moisture for one and one-half hours. The hard residue was broken up, 100 ml. of water was added, and the solid was collected and washed with water. After recrystallization from alcohol the nitrile formed fluffy needles which melted at 155.5–156°. The yield was practically quantitative.

Anal. Calc'd for $C_{19}H_{17}N$: C, 88.1; H, 6.6.
Found: C, 87.7; H, 6.6.

3-Chloro-9-(ω-bromoacetyl)retene. To a solution of 48 g. of 3-chloro-9-acetylretene in 1 liter of refluxing ether was added dropwise with stirring over a period of two hours a solution of 24.2 g. of bromine in 175 ml. of carbon tetrachloride. Heat was withdrawn and the solution was stirred for an additional hour. It was then allowed to stand overnight protected from light and moisture. After washing with water, dilute sodium bicarbonate solution, and again with water, the organic solution was dried with magnesium sulfate and concentrated to about 1100 ml. On cooling in an ice-bath 6 g. of white crystals separated (Fraction A) which melted at 125–138°. The filtrate was concentrated to 850 ml., and on chilling in an ice-bath yielded 2 g. of material melting at 106–132°. By successive evaporations, finally to dryness, other fractions were obtained which melted variously from 72–93°. All such fractions were separately fractionally recrystallized from ether, yielding a main fraction (32 g.), after removal of three sparingly soluble fractions, which melted at 86–88°. Concentration of the mother liquors from this yielded a second main fraction (6 g.) melting at 85–87°. Recrystallization of the above two main fractions from methanol gave 35 g. of the monobromo derivative which melted at 88–89°.

Anal. Calc'd for $C_{20}H_{18}BrClO$: C, 61.6; H, 4.7.
Found: C, 61.5; H, 4.7.

Faction A above was recrystallized thrice from ether and gave a substance melting at 168–173°. A further recrystallization from methanol gave material melting at 174–178° to a milky melt. Presumably this is largely the ω-dibromo derivative.

Anal. Calc'd for $C_{20}H_{17}Br_2ClO$: Total halogen: 41.7.
Found: Total halogen 38.9.

3-Chloro-9-(di-n-amylaminomethyl)retene methanol. To a solution of 15.1 g. of di-*n*-amylamine in 100 ml. of anhydrous ether was added a solution of 18.7 g. of 3-chloro-9-(ω-bromoacetyl)retene in 500 ml. of anhydrous ether. Dry nitrogen was passed through the solution to remove atmospheric oxygen and the stoppered container was left overnight at room temperature protected from light. After filtering off the precipitated diamylamine hydrobromide, dry hydrogen chloride was carefully passed over the surface of the chilled solution. The amino ketone hydrochloride separated as a white solid. It is important to avoid an excess of hydrogen chloride, as this causes the product to separate as an oil, rerefractory to crystallization. The hydrochloride formed plates melting at 193.5–195° on recrystallization from alcohol. It was not purified further for the next step. The yield was 15 g. (62%).

The above amino ketone hydrochloride (15 g.) was placed in a flask equipped with an eight-inch Vigreux column together with 50 ml. of dry isopropanol and 40 ml. of 3 *N* solution of aluminum isopropoxide in isopropanol. The mixture was heated in an atmosphere of dry nitrogen, and the acetone formed was distilled off from the steam-bath. Additional dry isopropanol was added occasionally to maintain the volume of the mixture. When the acetone was all removed (negative test with 2,4-dinitrophenylhydrazine in the distillate), the isopropanol was carefully removed under reduced pressure. The residual tan fluffy mass was dissolved in warm ether and washed with 2% sodium hydroxide solution and then with water. Crystallization of the amino carbinol hydrochloride was difficult. To a small chilled aliquot of the dried ether solution was added one-third of an equivalent of standard ethereal hydrogen chloride (based on an assumed 100% yield). Evaporation of the solvent yielded an oil which was dissolved in hot ethyl acetate Careful addition of ligroin followed by chilling and scratching produced seed crystals. This procedure was repeated with the main batch to which the seed crystals had been added, except that one equivalent of hydrogen chloride was used. Recrystallization of the crude product from ethyl acetate-ligroin gave 12 g. (80%) of the amino carbinol hydrochloride as white cubes melting at 162.5–163.5°.

Anal. Calc'd for $C_{30}H_{43}Cl_2NO$: C, 71.4; H, 8.7.
Found: C, 71.1; H, 8.6.

3-Chloro-9-(-diethylaminomethyl)retene methanol. This was prepared as was the above compound. Seed crystals were obtained directly from the ether test solution without use of ethyl acetate. The main batch crystallized from ethyl acetate-ligroin as white needles melting at 192.5–193.5°. The yield was 30%.

Anal. Calc'd for $C_{24}H_{31}Cl_2NO$: C, 68.6; H, 7.4.
Found: C, 68.4; H, 7.6.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

SYNTHESIS OF BZ-SUBSTITUTED QUINAZOLINES AND ANTIMALARIALS FROM THEM. A CONTRIBUTION TO THE CHEMISTRY OF QUINAZOLINE[1]

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Pamaquine (Plasmochin) and other derivatives of 8-aminoquinoline possess the apparently unique property, compared to other known antimalarial drugs, of permanently curing a high percentage of relapsing *Plasmodium vivax* cases when administered in conjunction with quinine (1). However these substances frequently possess undesirable toxic characteristics (1). Quinazoline derivatives have been reported (2, 3) to possess relatively low toxicity compared to quinoline derivatives. Magidson and Golovchinskaya (3), Sherrill and co-workers (4), and Price and co-workers (5) have described the synthesis of a number of quinazoline analogs of the highly effective 4-aminoquinoline antimalarials. The first workers report no antimalarial activity for the compounds prepared by them, although it should be noted in view of information now at hand (1), that their choice of substituents did not embrace the most effective ones. Of greater interest is the observation that the quinazoline analog of Chloroquine, 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinazoline (5), possesses a definite suppressive antimalarial action. This, taken together with the fact that the mechanism of action of the 8-aminoquinolines appears to differ markedly from that of the 4-aminoquinolines (1), warranted the synthesis of representative 8-aminoquinazolines.

During the course of the present work, a paper by Dewar (6) appeared in which the attempted synthesis of the quinazoline analog of Pamaquine is described. He devised a synthesis for 4-chloro-6-methoxy-8-nitroquinazoline, but attempts to remove the chlorine from this substance to yield the requisite 6-methoxy-8-aminoquinazoline (XV) were unsuccessful.

The only satisfactory synthesis for *bz*-substituted quinazolines previously reported is that of Riedel (7) which involves condensation of a derivative of *o*-nitrobenzaldehyde with formamide followed by reduction and cyclization of the intermediate *o*-nitrobenzylidene diformamide. Because of the inaccessibility of the properly substituted *o*-nitrobenzaldehyde an alternate synthesis was demanded in the present work. For this purpose the Niementowski reaction for the preparation of 4-quinazolones, as used simultaneously and independently by Dewar (6), seemed applicable provided a means could be found for the conversion of the quinazolone to the quinazoline. In order to study this problem the conversion of 4-quinazolone to quinazoline was first investigated because of readily available materials, and the results of this study were then applied to the 8-aminoquinazolines.

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[2] National Research Council Pre-doctoral Fellow.

4-Quinazolone (IV) is readily converted to 4-chloroquinazoline (VII). Removal of the chlorine in this compound by catalytically activated hydrogen was readily accomplished. However the course of the reduction of this substance as well as of other 4-chloroquinazolines was profoundly influenced by the experimental conditions used. The solvent in which the reactions are carried out appears to be the factor controlling the reduction. Thus using the palladium on calcium carbonate catalyst of Busch and Stöve (8) in hydroxylated solvents such as alcohol, or ethylene glycol monomethyl ether (Methyl Cellosolve) reduction proceeded rapidly with the absorption of two moles of hydrogen and the formation of 3,4-dihydroquinazoline (X). In non-hydroxylated solvents such as dioxane, the first mole of hydrogen was absorbed much more slowly and shortly thereafter hydrogen absorption practically stopped, possibly because of the insolubility of the hydrochloride of the reduction product. However, this insolubility was not the primary cause of the slowing up of the reduction, for in the same solvent in the presence of sodium acetate or potassium hydroxide, the free base of the product remained in solution and the second mole of hydrogen was absorbed linearly but much more slowly than was the first. By stopping the reduction after the absorption of one mole of hydrogen it was possible to isolate a satisfactory amount of pure quinazoline. When carried out in representative secondary and tertiary alcohols, *iso*propanol and *tert*-butanol, the course of the reduction was not altered qualitatively, although the rate was slower in the secondary and still slower in the tertiary alcohol. The use of Raney nickel catalyst in dioxane and methanol resulted in incomplete reduction undoubtedly because of inactivation of the catalyst by the liberated hydrochloric acid. When the 4-chloroquinazolines were reduced in methanol or ethanol in the presence of potassium hydroxide over Raney nickel or palladium on calcium carbonate, the products were the corresponding 4-alkoxyquinazolines. In contrast to the behavior of quinazoline itself no tendency toward the absorption of a second mole of hydrogen was noted under these conditions, and further the 4-methoxyquinazolines when shaken with fresh catalyst and hydrogen failed to absorb hydrogen with the formation of the 3,4-dihydro derivatives. Curves representing the course of the reduction of a number of 4-chloroquinazolines are shown in Figures 1, 2, and 3.

The results obtained in the study of the reduction of 4-chloroquinazoline were readily applicable to the reduction of 8-nitro-4-chloroquinazoline (VIII), 6-methoxy-8-nitro-4-chloroquinazoline (IX), and 6-nitro-4-chloroquinazoline (XX). Over palladium on calcium carbonate all of these substances were reduced to the dihydroquinazolines with simultaneous reduction of the nitro group when the reduction was carried out in methanol or Methyl Cellosolve. In dioxane, apparently the rate of the reduction slackened markedly after the quinazoline had been reached, but due to the presence of the nitro group it was more difficult to stop the reduction at the quinazoline stage than in the reduction of 4-chloroquinazoline itself. Accordingly, it was more convenient to allow the

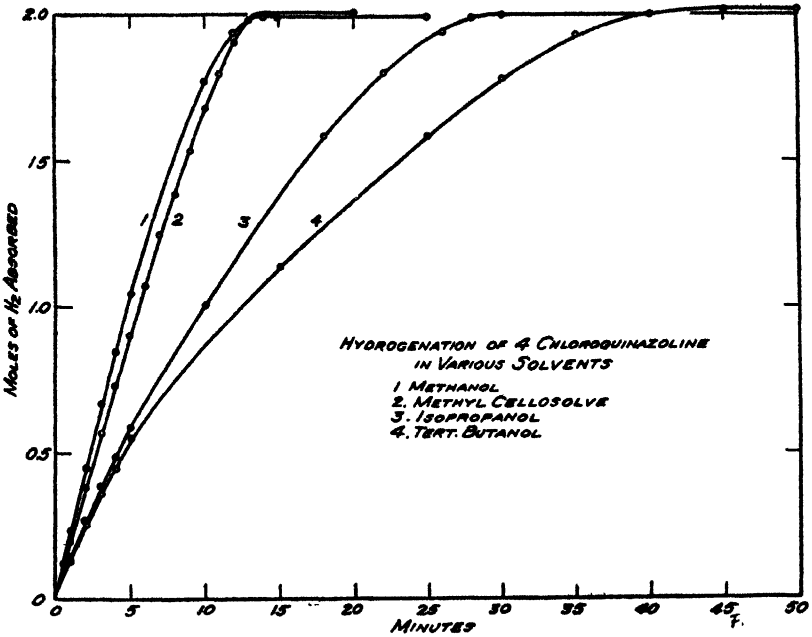

2.0
1.5
1.0
0.5
0
Moles of H_2 Absorbed
1
2
3
4
Hydrogenation of 4 Chloroquinazoline
in Various Solvents
1 Methanol
2. Methyl Cellosolve
3. Isopropanol
4. Tert. Butanol
0
5
10
15
20
25
30
35
40
45
50
Minutes

FIG. 1

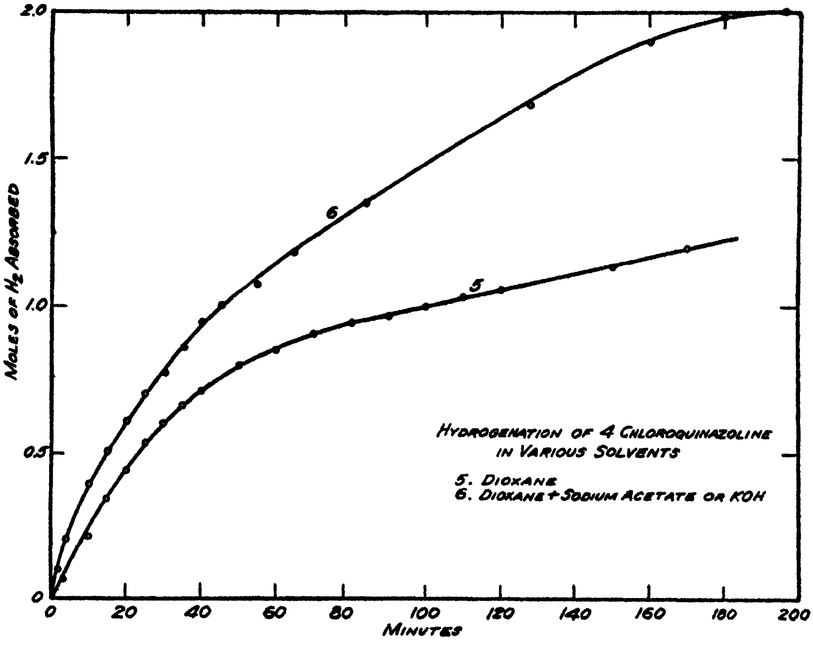

2.0
1.5
1.0
0.5
0
Moles of H_2 Absorbed
6
5
Hydrogenation of 4 Chloroquinazoline
in Various Solvents
5. Dioxane
6. Dioxane + Sodium Acetate or KOH
0
20
40
60
80
100
120
140
160
180
200
Minutes

FIG. 2

reduction to proceed to the amino-3,4-dihydroquinazolines and subsequently to dehydrogenate the latter back to the quinazolines with potassium ferricyanide. This method has apparently been used but once in the past, by Gabriel (9). The action of ferricyanide appears to be quite specific in this respect, and no signs of oxidation in the benzene ring, such as might have been expected by virtue of the presence of the amino group, were noted. In this way the 4-chloroquinazolines were converted to quinazolines in 65–86% over-all yields without isolation of the intermediate dihydroquinazoline. Prior to the successful dehydrogenation of the free aminoquinazolines, blocking of the 8-amino group was believed to be necessary. Accordingly 8-(*p*-toluenesulfonamido)quinazolone-4 was prepared.

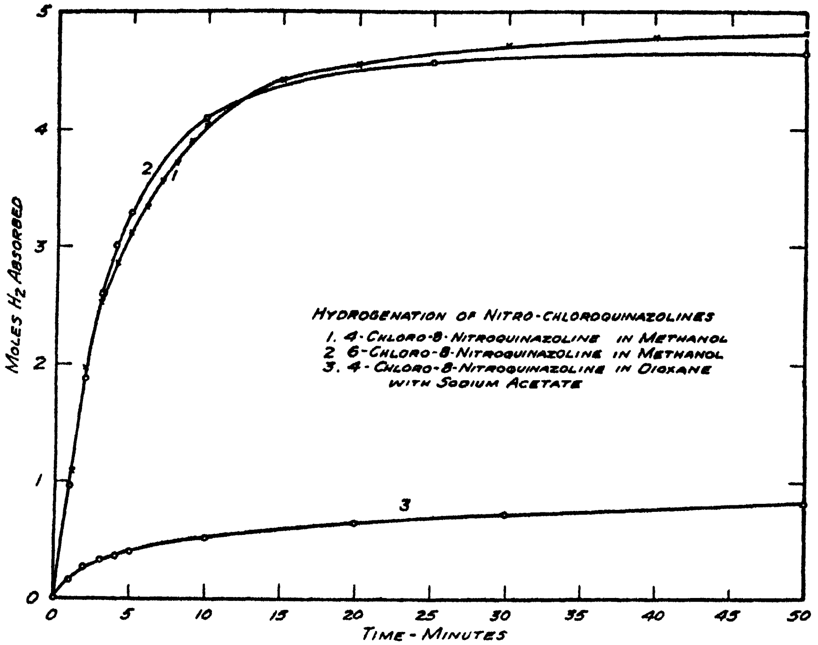


FIG. 3

On attempted conversion of this to the 4-chloro compound, no crystalline material was isolated, although the glassy product of the reaction was reconverted to 8-(*p*-toluenesulfonamido)quinazolone-4 on boiling with water. This approach was dropped when the dehydrogenation was carried out successfully on the free amine.

In the above studies it was found to be difficult to distinguish between dihydroquinazolines and quinazolines on the basis of the usual physical properties (color, solubilities, etc.) and elementary analyses. Accordingly a study of additional properties of the two series of compounds was made in order to provide a basis for such differentiation. Ultraviolet absorption studies failed to provide a sharp means for distinguishing the two. The curves for various quinazolines and dihydroquinazolines are shown in Figure 4. The similarity of the curves for quinazoline and 3,4-dihydroquinazoline parallels the similarity between the curves for naphthalene and 1,2-dihydronaphthalene (10).

Potentiometric titration of the various quinazoline derivatives yielded more valuable information, by which it was possible to distinguish conveniently between the quinazolines and their dihydro derivatives. Titration curves for a number of such substances are shown in Figure 5, and the dissociation constants are shown in Table I. Whereas quinazoline itself is a weak base, 3,4-dihydroquinazoline as would be expected is a relatively stronger base, the basicity of which is largely destroyed on acetylation. Introduction of an amino group into the 8-position of quinazoline or a 3,4-dihydroquinazoline does not affect the basic ionization constant of the parent substance appreciably. Likewise introduction of an amino group into the 6-position of quinazoline exerts no effect on the dissociation constant of the parent compound. This is in agreement with similar effects observed on the introduction of amino groups in the corresponding positions in acridine (11).

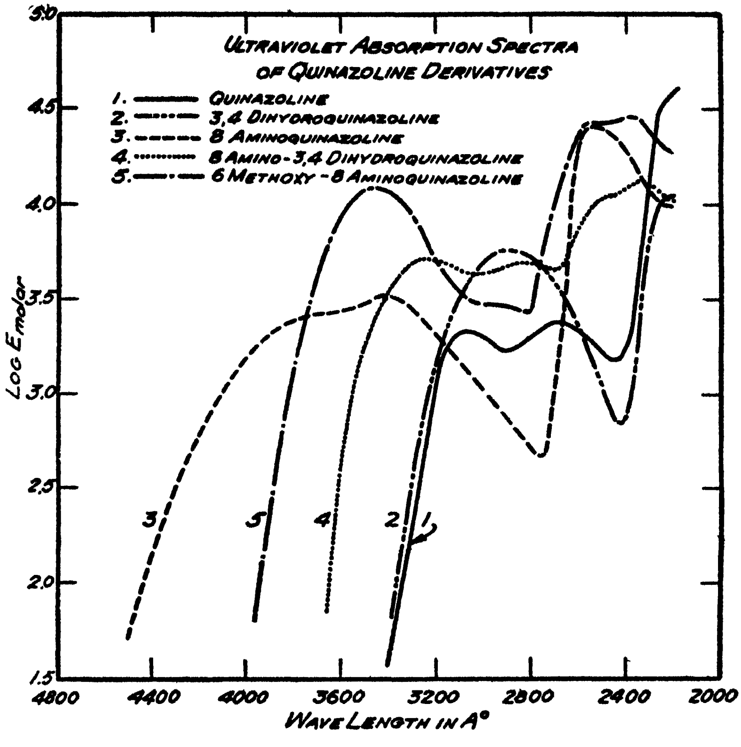


FIG. 4

Although it is also possible to distinguish the aminodihydroquinazolines from the aminoquinazolines by elementary analyses of their respective acetyl derivatives, the potentiometric titration method is preferred because of its simplicity and the unequivocal nature of the results.

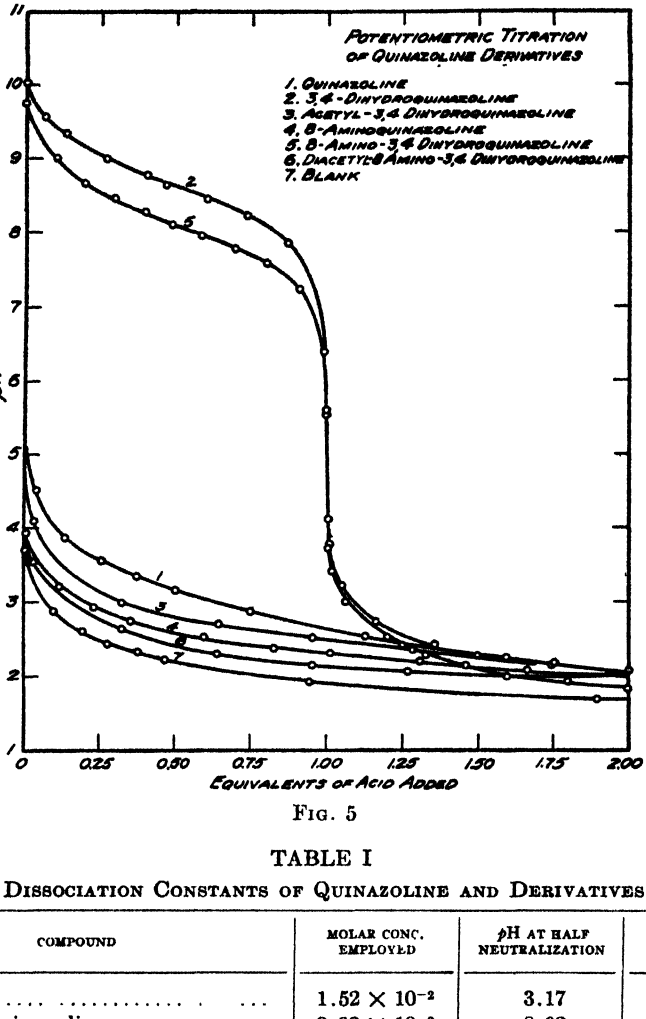


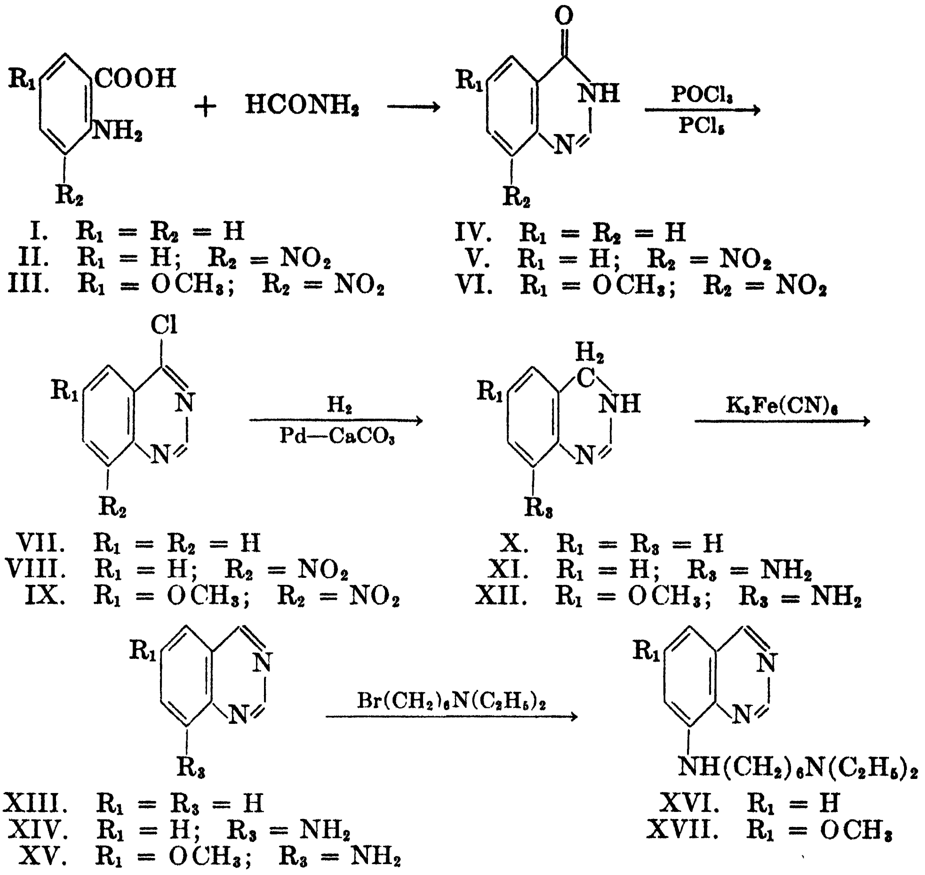
FIG. 5

TABLE I

DISSOCIATION CONSTANTS OF QUINAZOLINE AND DERIVATIVES

COMPOUND	MOLAR CONC. EMPLOYED	pH AT HALF NEUTRALIZATION	K$_b$ AT 27°C
Quinazoline	1.52×10^{-2}	3.17	2×10^{-11}
3,4-Dihydroquinazoline	3.02×10^{-2}	8.62	6×10^{-6}
Acetyl-3,4-dihydroquinazoline	1.56×10^{-2}	2.81	7×10^{-12}
8-Aminoquinazoline	1.60×10^{-2}	2.61	3×10^{-12}
8-Amino-3,4-dihydroquinazoline	2.02×10^{-2}	8.08	2×10^{-6}
Diacetyl-8-amino-3,4-dihydroquinazoline	1.20×10^{-2}	2.43	1×10^{-12}
6-Aminoquinazoline	1.50×10^{-2}	3.22	2×10^{-11}
6-Methoxy-8-aminoquinazoline	1.51×10^{-2}	4.06	2×10^{-10}
4-Methoxy-8-aminoquinazoline	2.28×10^{-2}	2.47	2×10^{-12}

As mentioned above, the various quinazolones were prepared by application of the Niementowski reaction (12) as represented by formulas I–VI. The requisite anthranilic acids I–III were prepared by published methods with some alterations and improvements. 4-Quinazolone (IV) and 4-chloroquinazoline (VII) have been described previously; 8-nitro-4-quinazolone (V) and 4-chloro-8-nitroquinazoline (VIII) are new, while 6-methoxy-8-nitro-4-quinazolone (VI) and 4-chloro-6-methoxy-8-nitroquinazoline (IX) were described by Dewar (6), although in not too great detail, during the course of the present work. The dihydroquinazolines (XI and XII) and the quinazolines (XIV and XV) are new.



I. $R_1 = R_2 = H$
II. $R_1 = H; \ R_2 = NO_2$
III. $R_1 = OCH_3; \ R_2 = NO_2$

IV. $R_1 = R_2 = H$
V. $R_1 = H; \ R_2 = NO_2$
VI. $R_1 = OCH_3; \ R_2 = NO_2$

VII. $R_1 = R_2 = H$
VIII. $R_1 = H; \ R_2 = NO_2$
IX. $R_1 = OCH_3; \ R_2 = NO_2$

X. $R_1 = R_3 = H$
XI. $R_1 = H; \ R_3 = NH_2$
XII. $R_1 = OCH_3; \ R_3 = NH_2$

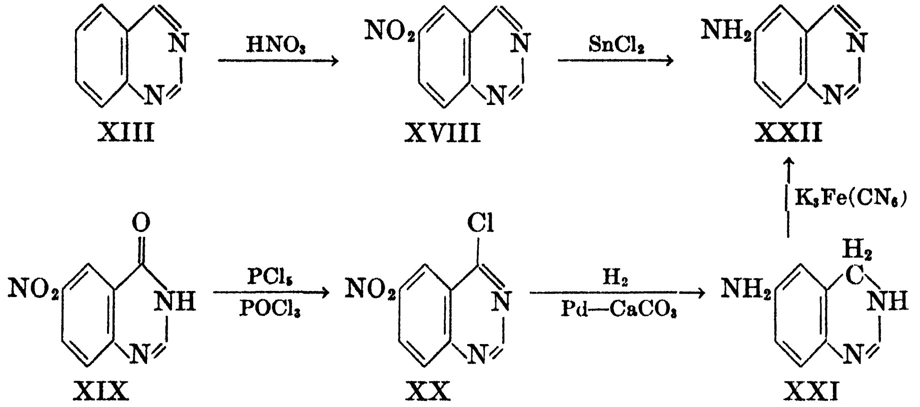
XIII. $R_1 = R_3 = H$
XIV. $R_1 = H; \ R_3 = NH_2$
XV. $R_1 = OCH_3; \ R_3 = NH_2$

XVI. $R_1 = H$
XVII. $R_1 = OCH_3$

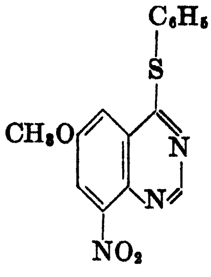
The general properties of the 8-aminoquinazolines have been discussed in part above. In addition, they show the normal reactions of aromatic primary amines and resemble 8-aminoquinolines. Thus, they can be readily diazotized in acid solution, and the resulting diazonium salts couple readily with cold alkaline β-naphthol or an acid solution of β-naphthylamine, to yield characteristic red or orange azo dyes.

8-(6-Diethylaminohexylamino)quinazoline (XVI) and 6-methoxy-8-(6-diethylaminohexylamino)quinazoline (XVII) were prepared by condensation of XIV and XV with 6-diethylaminohexyl bromide (13).

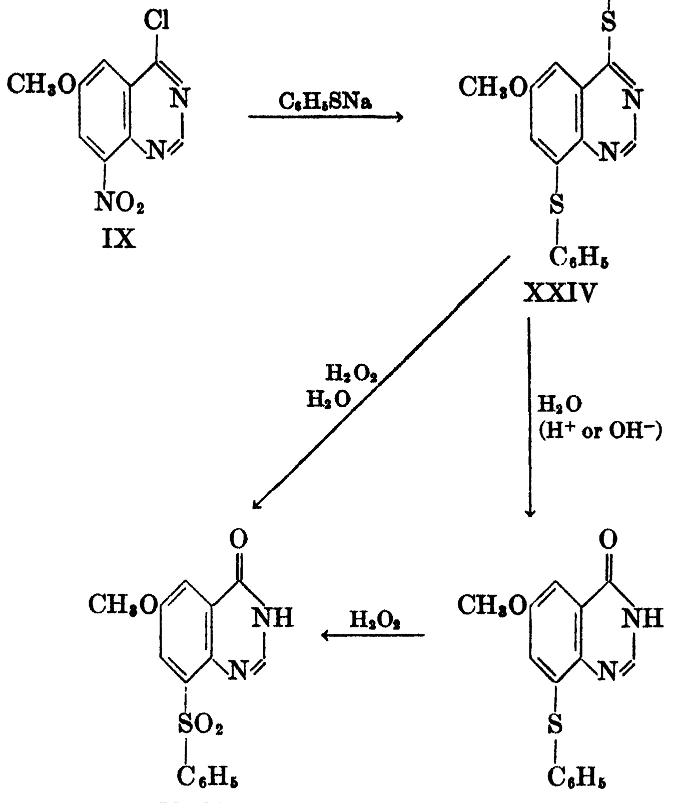
Since quinoline on nitration furnishes a mixture of 5- and 8-nitroquinoline (14) and since isoquinoline yields exclusively 5-nitroisoquinoline (15) it was of interest to examine the behavior of quinazoline on nitration, for it has been regarded in the past as both a quinoline and an isoquinoline, and a more convenient route to 8-aminoquinazoline conceivably might be offered by this scheme. To our surprise, the only mononitro compound isolated from the nitration of quinazoline proved to be 6-nitroquinazoline (XVIII). The position of the nitro group in XVIII was shown by the identity of 6-aminoquinazoline (XXII), obtained from XVIII by reduction, with an authentic sample of 6-aminoquinazoline prepared from 6-nitro-4-quinazolone, in which the position of the nitro group has been established by Magidson and Golovchinskaya (3), by the method used in the synthesis of the above quinazolines, (XIX–XXII).



Before the successful conversion of the 4-chloroquinazolines to quinazolines had been worked out an attempt was made to prepare 6-methoxy-8-nitroquinazolyl-4-phenyl sulfide (XXIII) preparatory to reduction of the sulfide to the quinazoline according to the method of Mozingo and co-workers (16). In the reaction of 4-chloro-6-methoxy-8-nitroquinazoline (IX) with sodium thiophenolate, a striking replacement of the nitro group by a thiophenyl group occurred, in addition to the expected reaction at the 4-position, to yield 6-methoxy-4,8-quinazolyl-*bis*(phenyl sulfide) (XXIV). This structure was confirmed by a study of the reactions of XXIV, and in addition, new information concerning the reactivity of an aryl sulfide group in the 4-position of quinazoline was obtained. When the disulfide, XXIV, was oxidized with hydrogen peroxide in dilute acetic acid solution in an attempt to prepare the corresponding disulfone, the quinazolone sulfone (XXV) was obtained. This substance was soluble in alkaline solution, from which it was concluded that the sulfide group in the 4-position had been removed. While it is true that the 8-sulfide group conceivably could be lost to yield a phenol, it is not likely that such a substance would remain unattacked in the presence of hydrogen peroxide. Confirmation of this interpretation was obtained by a study of the hydrolysis of the disulfide XXIV. Under relatively mild conditions one of the sulfide groups was removed yielding an alkali-soluble, high-melting product to which the structure XXVI is assigned.



XXIII



Oxidation of XXVI with hydrogen peroxide yielded XXV. Since the experimental conditions leading to the formation of XXV were as mild or milder than those under which XXVI was formed, the structure assigned to XXV appears to be reasonable.

In the past it has been suggested by various workers that quinazoline can be regarded either as quinoline or isoquinoline. In view of the observations made in the present work as well as several other observations reported in the literature, we believe that quinazoline can better be regarded as a cyclic amidine. Further study of quinazoline derivatives in the light of this interpretation is in progress.

EXPERIMENTAL

All melting points are corrected unless noted otherwise.

8-Nitroquinazolone-4 (V). Sixty grams of 3-nitroanthranilic acid, prepared according to Chapman and Stevens (17), and 120 g. of redistilled formamide were heated in an open beaker in an oil-bath at an inside temperature of 155–160° for six hours. The dark residue, after cooling, was pulverized and washed with 5% sodium bicarbonate solution, then with water, and dried, yielding 42 g. (67%) of crude material which melted at 240–248°. It was recrystallized from nitrobenzene (100 ml. per 15 g.) with liberal use of decolorizing carbon.

The recrystallized material was washed with ether to remove residual nitrobenzene. Fifty per cent aqueous pyridine may also be used for recrystallization. The quinazolone formed pale yellow needles which melted at 250–251°.

Anal. Calc'd for $C_8H_5N_3O_3$: C, 50.3; H, 2.6.
Found: C, 50.2; H, 2.7.

On acidification of the bicarbonate washings, 18 g. (30%) of 3-nitroanthranilic acid was recovered.

8-Aminoquinazolone-4. A mixture of 12 g. of 8-nitroquinazolone-4, 90 g. of sodium sulfide nonahydrate, and 30 ml. of water was warmed with shaking until it was sufficiently liquid to boil, and was then heated under reflux for five hours. The solution was cooled and filtered, the filtrate was diluted to twice its volume with water and then neutralized with acetic acid. The precipitated 8-aminoquinazolone-4, contaminated with sulfur was collected, washed with water, and recrystallized from water (charcoal) to yield 7.7 g. (76%) of colorless needles which melted at 260–261°, dec. with sintering at 235–237°.

Anal. Calc'd for $C_8H_7N_3O$: C, 59.7; H, 4.4.
Found: C, 59.8; H, 4.2.

8-(p-Toluenesulfonamido)quinazolone-4. To a solution of 6.8 g. of 8-aminoquinazolone-4 in 50 ml. of dry pyridine was added a solution of 8.4 g. of *p*-toluenesulfonyl chloride in pyridine. After fifteen minutes at room temperature, the solution was heated for five minutes on the steam-bath, cooled, and poured into water. The pink solid was recrystallized from alcohol-pyridine mixtures, yielding 11 g. (83%) of colorless prisms which melted at 268–269°.

Anal. Calc'd for $C_{15}H_{13}N_3O_3S$: C, 57.1; H, 4.1.
Found: C, 57.3; H, 3.9.

Upon boiling the above substance with an equimolar amount of phosphorus pentachloride and ten times its weight of phosphorus oxychloride, a clear yellow solution was formed in ten minutes. After boiling for an additional twenty minutes the solvent was removed under reduced pressure leaving a hard yellow glassy residue which was insoluble in hot acetone, petroleum ether, toluene, and chloroform When boiled with water it was converted into 8-(*p*-toluenesulfonamido)quinazolone-4. It was therefore concluded that the glass was probably the desired 4-chloro-8-(*p*-toluenesulfonamido)quinazoline, although it was not investigated further.

4-Chloro-8-nitroquinazoline (VIII). A mixture of 12 g. of 8-nitroquinazolone-4, 15 g. of phosphorus pentachloride, and 60 ml. of phosphorus oxychloride was heated under reflux until solution was complete (one hour) and then for an additional half hour. The solution was cooled slowly and the yellow needles which separated were washed free of phosphorus halides with anhydrous ether. The yield of 4-chloro-8-nitroquinazoline, melting at 192–195° was 11.9 g. (91%). After several recrystallizations from toluene the substance formed square plates which melted at 197–197.5°.

Anal. Calc'd for $C_8H_4ClN_3O_2$: C, 45.8; H, 1.9.
Found: C, 46.1; H, 2.0.

4-Methoxy-8-nitroquinazoline. A solution of 1 g. of 4-chloro-8-nitroquinazoline in sodium methoxide prepared from 0.16 g. of sodium and 5 ml. of absolute methanol was boiled for ten minutes, cooled, and poured into cold water. The solid which separated was recrystallized from methanol and from carbon tetrachloride, yielding fine colorless needles which melted at 132.5–133°. The yield was 90%.

Anal. Calc'd for $C_9H_7N_3O_3$: C, 52.7; H, 3.4.
Found: C, 52.8; H, 3.4.

4-Methoxy-8-aminoquinazoline. In this and all subsequent catalytic reductions reported in this paper, the palladium hydroxide on calcium carbonate catalyst of Busch and Stöve (8) was used unless stated otherwise. The catalyst contained 40 mg. of palladium per gram of catalyst It was either reduced to palladium before addition of the substance to be reduced or both catalyst and reductant were added together at the start and reduced without interruption.

One gram of previously reduced catalyst and 0.2 g. of 4-methoxy-8-nitroquinazoline were suspended in 5 ml. of absolute methanol and shaken under 25 lb. pressure of hydrogen. Reduction was complete after ten minutes, when threee quivalents of hydrogen had been absorbed and no further absorption took place in the succeeding ten minutes. The filtrate from the catalyst was concentrated to dryness and the residue was recrystallized from water or dilute methanol, yielding 4-methoxy-8-aminoquinazoline as fine colorless needles melting at 153.5–154°.

Anal. Calc'd for $C_9H_9N_3O$: C, 61.7; H, 5.2.
Found: C, 61.3; H, 5.2.

3,4-Dihydro-8-aminoquinazoline (XI). A suspension of 5 g. of 4-chloro-8-nitroquinazoline and 5 g. of catalyst in 50 ml. of absolute methanol was shaken under 30 lb. pressure of hydrogen. In ten minutes substantially five equivalents of hydrogen had been absorbed and absorption stopped. The filtrate from the catalyst was concentrated to 10–15 ml. when crystals began to separate. After dilution with several volumes of water, the mixture was made strongly alkaline and extracted with ether. After washing the extract with water, removal of the solvent left 2.5 g. of a pale yellow solid which melted at 88–95°. 3,4-Dihydro-8-aminoquinazoline sublimes slowly at 70–80° at 0.2 mm. and may be recrystallized from benzene-petroleum ether (3:2). It forms fine colorless needles which melt at 98.5–99°. The substance is quite unstable when exposed to air and turns dark and gummy after several days. If kept in a vacuum under nitrogen it may be stored for months.

Anal. Calc'd for $C_8H_9N_3$: C, 65.3; H, 6.2.
Found: C, 65.6; H, 6.0.

When the above reduction was carried out at 60° or when the reaction mixture was heated before reduction, none of the dihydro derivative was obtained. Rather, a quantitative yield of 4-methoxy-8-aminoquinazoline resulted.

Curves showing the rate of hydrogen uptake in the reduction of various quinazoline derivatives are shown in Figures 1, 2, and 3. The products of reduction isolated are shown in Table II.

3-Acetyl-3,4-dihydroquinazoline.[3] On refluxing a mixture of 0.5 g. of 3,4-dihydroquinazoline with 1 ml. of acetic anhydride in 10 ml. of dry benzene for one hour and concentration to dryness, the acetyl derivative was obtained as colorless hygroscopic needles which melted at 131–132° after recrystallization from petroleum ether-benzene (1:3). On exposure to the air, the substance rapidly hydrated, and the water thus acquired was retained on drying *in vacuo* at 100°.

Anal. Calc'd for $C_{10}H_{10}N_2O \cdot H_2O$: C, 62.5; H, 6.3.
Found: C, 62.2; H, 6.1.

3-Acetyl-8-acetamino-3,4-dihydroquinazoline.[3] Acetylation of 3,4-dihydro-8-aminoquinazoline as above gave the diacetyl derivative, which formed needles from benzene-petroleum ether (9:1) and melted at 167–168°.

Anal. Calc'd for $C_{12}H_{13}N_3O_2$: C, 62.3; H, 5.7; N, 18.2.
Found: C, 62.5; H, 5.4; N, 17.9.

8-Aminoquinazoline (XIV). To a solution of 1 g. of 3,4-dihydro-8-aminoquinazoline in 50 ml. of warm water was added 10 ml. of 33% potassium hydroxide solution. A solution of 5 g. of potassium ferricyanide in 40 ml. of warm water was then added slowly. The dark red solution was allowed to stand for five minutes, and then treated with 50 ml. of 33% potassium hydroxide and extracted with ether. After drying the extract, removal of the solvent left 0.76 g. of red crystals which melted at 145–150°. After purification by sublimation above 100° and crystallization from water, benzene, or chloroform, pure 8-aminoquinazoline was obtained as long, flat, yellow needles which melted at 150–150.5°.

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[3] Although the structure assigned to the acetyl derivative of dihydroquinazoline, as well as to its 8-acetamino derivatives, is that of 3-acetyl-3,4-dihydroquinazoline, this is on a purely arbitrary basis. The possibility that these are 1-acetyl-1,4-dihydroquinazoline derivatives exists. However, the ultraviolet absorption curves by analogy with those of the dihydronaphthalenes support the structure as indicated.

Anal. Calc'd for $C_8H_7N_3$: C, 66.2; H, 4.9.
Found: C, 66.3; H, 4.8.

In practice it was found to be more convenient to dehydrogenate the dihydro derivative directly as obtained from the reduction rather than to isolate it. Thus, in a typical experiment 8 g. of 4-chloro-8-nitroquinazoline was reduced in cold methanol. The filtrate from the catalyst was concentrated to 10–15 ml. *in vacuo* and diluted with 200 ml. of water. To this was added 60 ml. of 33% potassium hydroxide solution followed by a solution of 26 g. of potassium ferricyanide in 200 ml. of warm water. After five minutes the reaction mixture was worked up as before giving 75–85% of 8-aminoquinazoline.

TABLE II

CATALYTIC REDUCTION OF 4-CHLOROQUINAZOLINE DERIVATIVES

COMPOUND	SOLVENT	EQUIVS. OF H_2 ABSORBED	TIME IN MINUTES	PRODUCT ISOLATED	% YIELD
4-Chloroquinazoline	Methanol	2.0	14	3,4-Dihydroquinazoline	90
4-Chloroquinazoline	Methyl Cellosolve	2.0	14	3,4-Dihydroquinazoline	90
4-Chloroquinazoline	*Iso*propanol	2.0	30	3,4-Dihydroquinazoline	93
4-Chloroquinazoline	*Tert.*-butanol	2.0	40	3,4-Dihydroquinazoline	—
4-Chloroquinazoline	Dioxane	1.2	170	Mixture	—
4-Chloroquinazoline	Dioxane[a]	2.0	180	3,4-Dihydroquinazoline	84
4-Chloroquinazoline	Dioxane[a]	1.0[b]	53	Quinazoline	51
4-Chloro-8-nitroquinazoline	Methanol	4.8	50	8-Amino-3,4-dihydroquinazoline	80
4-Chloro-8-nitroquinazoline	Dioxane[a]	4.0[b]	260	8-Aminoquinazoline	24
4-Chloro-6-nitroquinazoline	Methyl Cellosolve	4.7	50	6-Aminoquinazoline[c]	65
4-Chloro-6-methoxy-8-nitroquinazoline	Methanol	4.7	60	6-Methoxy-8-aminoquinazoline[c]	67

[a] In the presence of sodium acetate or potassium hydroxide.
[b] Uncompleted reduction stopped at this point.
[c] After $K_3Fe(CN)_6$ oxidation of initial reduction product.

Eight grams of 4-chloro-8-nitroquinazoline was shaken with 10 g. of catalyst in 100 ml. of dry dioxane containing 8 g. of potassium hydroxide under 30 lb. hydrogen pressure. The reduction was arbitrarily stopped after about three hours when 4 equivalents of hydrogen had been absorbed. From the reduction products 1.2 g. (22%) of 8-aminoquinazoline melting at 145–148° was obtained by sublimation.

8-Acetaminoquinazoline. A mixture of 0.5 g. of 8-aminoquinazoline, 1 ml. of acetic anhydride and 10 ml. of dry benzene was boiled for one hour. Recrystallization from water of the residue obtained on concentration of the reaction mixture to dryness gave 8-acetaminoquinazoline as pale yellow needles which melted at 161–162°. After drying at 100° for two hours *in vacuo*, the substance still apparently retained a molecule of water of crystallization.

Anal. Calc'd for $C_{10}H_9N_3O \cdot H_2O$: C, 58.5; H, 5.4.
Found. C, 58.8; H, 5.3.

4-Chloro-6-methoxy-8-nitroquinazoline (IX). This was prepared by a nine-step synthesis from *m*-cresol substantially by the method the last steps of which were published by Dewar (6) while this work was in progress. Our results may be summarized as follows:

(a) *2-Amino-5-hydroxytoluene* was prepared from *m*-cresol by nitrosation and reduction following the procedure of Kremers, Wakeman, and Hixon (18) for the preparation of aminothymol. The over-all yield from reactions using one mole of *m*-cresol was 85–89% of air-dried material melting at 168–171°. Smith and Irwin (19) who prepared the substance by reduction of the azo compound obtained by coupling *m*-cresol and diazotized *p*-nitroaniline, report the melting point to be 173–176°.

(b) *2-Acetamino-5-hydroxytoluene.* This was prepared by a modification of the method of Bogert and Connitt (20). To a suspension of 200 g. of crude 2-amino-5-hydroxytoluene in 2 l. of water was added with shaking a mixture of 400 ml. of acetic anhydride and 80 ml. of acetic acid. After heating the mixture to boiling with charcoal, it was filtered and cooled. The total yield of 2-acetamino-5-hydroxytoluene after working the mother liquors was 220 g. (82%). The material melted at 123–125° after sintering at 80°. Bogert and Connitt (20) report 125°.

(c) *2-Acetamino-5-methoxytoluene.* Methylation of the above compound with dimethyl sulfate in alkaline solution by the procedure of Heidelberger and Jacobs (21) gave 97% of 2-acetamino-5-methoxytoluene as colorless plates melting at 132.5–133.5° after recrystalliaction from 30% alcohol. Friedländer (22) gives the melting point as 134°.

(d) *3-Nitro-2-acetamino-5-methoxytoluene.* When Dewar's procedure (6) was followed a much lower yield of the nitro compound than that reported by him was obtained. A considerable amount of a higher-melting product was obtained as yellow needles which melted at 248–250°. Although this was not investigated further it undoubtedly was a dinitro derivative. When 2-acetamino-5-methoxytoluene was nitrated according to Dewar (6) except that the reaction was allowed to proceed for thirty minutes at −5° rather than for three hours at 0° as described by him, 60–65% of the mononitro compound melting at 187–188° after recrystallization from alcohol was obtained. Dewar (6) reports the melting point as 187°.

(e) *3-Nitro-5-methoxyanthranilic acid* Oxidation of the methyl group in the above substance with potassium permanganate and hydrolysis of the acetamino group substantially according to Dewar (6) gave the anthranilic acid readily in good yield.

(f) *6-Methoxy-8-nitroquinazolone-4* (VI). By heating equal weights of 3-nitro-5-methoxyanthranilic acid and formamide for three hours at an inside temperature of 160–165°, the quinazolone was obtained in 67–72% yield. After two recrystallizations from 20% aqueous pyridine it melted at 275–277° (dec.) and was sufficiently pure for the subsequent hydrochlorination. Dewar (6) gives the melting point as 270°.

Treatment of the above quinazolone with phosphorus pentachloride and phosphorus oxychloride as in the preceding case gave 4-chloro-6-methoxy-8-nitroquinazoline (IX) as pale yellow needles melting at 148–148.5° after recrystallization from toluene. Dewar (6) reports the melting point as 144–147°.

Anal. Calc'd for $C_9H_6ClN_3O_3$: C, 45.1; H, 2.5.

Found: C, 45.0; H, 2.5.

4,6-Dimethoxy-8-nitroquinazoline. Reactions of 4-chloro-6-methoxy-8-nitroquinazoline with sodium methoxide as in the preceding case gave 92% of pale yellow needles which melted at 165–165.5°.

Anal. Calc'd for $C_{10}H_9N_3O_4$: C, 51.1; H, 3.9.

Found: C, 51.0; H, 3.9.

4,6-Dimethoxy-8-aminoquinazoline. On catalytic reduction by the standard procedure the above nitro compound absorbed three moles of hydrogen and showed no tendency toward further hydrogen uptake with reduction of the nucleus. The aminoquinazoline was isolated as before and formed yellow plates which melted at 149–151°. The substance was so unstable that satisfactory analytical figures could not be obtained. On exposure to air it rapidly turned green and became gummy.

6-Methoxy-8-aminoquinazoline (XV). This was prepared by reduction of the nitro compound to the 3,4-dihydro derivative in cold methanol and dehydrogenation of the latter without isolation exactly as in the case of 8-aminoquinazoline. For the final extraction chloroform was preferable to ether. The yield of fine colorless needles melting at 156–156.5° was 65%.

Anal. Calc'd for $C_9H_9N_3O$: C, 61.7; H, 5.2.
Found: C, 62.0, 62.0; H, 5.3, 5.4.

When the above reduction was carried out at 60° or when potassium hydroxide was present during the reduction, the only product isolated was 60–90% of 4,6-dimethoxy-8-aminoquinazoline.

6-Methoxy-8-acetaminoquinazoline. Acetylation of the amine by boiling it with acetic anhydride in benzene gave the acetyl derivative, which formed feathery needles from benzene-alcohol, and melted at 215–216° (dec.) with sintering at 205–206°.

Anal. Calc'd for $C_{11}H_{11}N_3O_2$: C, 60.8; H, 5.1; N, 19.3.
Found: C, 60.7; H, 5.0; N, 19.0.

8-(6-Diethylaminohexylamino)quinazoline (XVI). A mixture of 17.4 g. of 8-aminoquinazoline, 44.4 g. of 6-diethylaminohexyl bromide hydrobromide, and 27.2 g. of fused sodium acetate was heated under reflux in 140 ml. of absolute alcohol for sixty hours. After cooling, the solution was poured into 800 ml. of water, made strongly alkaline, and extracted with five portions of ether. The combined ether extracts were washed three times with 300 ml. of water containing 10% acetic acid and 10% sodium acetate (*p*H 4). After drying the ether solution, 10 g. (57%) of 8-aminoquinazoline was recovered.

The aqueous acetate extract was made strongly alkaline and extracted with ether, and after drying the extracts and removal of the solvent, the crude drug remained as a viscous dark oil. The oil was distilled under reduced pressure from a Claisen flask with a wide side-arm. After a forerun boiling at 125–140° at 25 mm., about 1 g. of 8-aminoquinazoline sublimed at a bath temperature of 160–170° at 0.3 mm. The drug base distilled at 165–175° at 0.3 mm. as a viscous yellow oil. The yield was 5.4 g. or 56% based on the 8-aminoquinazoline not recovered. After two more distillations under nitrogen it boiled at 170–173° at 0.1 mm.

Anal. Calc'd for $C_{18}H_{28}N_4$: C, 72.0; H, 9.4.
Found: C, 72.1; H, 9.2.

The material was found to possess a homogeneity of 97 ± 2 % when examined by the method of Craig (23).

A solution of 3.43 g. of the pure base in 300 ml. of dry ether was treated slowly with shaking with a solution of 1.44 g. of oxalic acid dihydrate in 25 ml. of absolute alcohol. After cooling to 0° the solid oxalate was collected, washed with ether, and dried immediately *in vacuo*. If air-dried, the hygroscopic salt tends to become sticky and turns orange. If thoroughly dry, the salt forms a stable, pale yellow solid melting at 90–92°.

Anal. Calc'd for $C_{20}H_{30}N_4O_4$: C, 61.5; H, 7.7.
Found: C, 61.3, H, 8.0.

Neither this compound nor the one described in the next paragraph showed appreciable activity when tested against *lophurae* malaria in the duck.[4]

6-Methoxy-8-(6-diethylaminohexylamino)quinazoline (XVII). This was prepared exactly as was the above substance. The recovery of unreacted 6-methoxy-8-aminoquinazoline was 40%. The drug base was considerably less stable than was the preceding one and, after two distillations under nitrogen, it boiled at 178–180° at 0.06 mm. The yield was 30% based on nucleus not recovered. The pale yellow oil was converted directly to the oxalate which formed a pale yellow powder melting at 101–103°.

Anal. Calc'd for $C_{21}H_{32}N_4O_5$: C, 60.0; H, 7.7.
Found: C, 60.2; H, 7.6.

6-Nitroquinazoline (XVIII). Two grams of quinazoline was shaken with 10 ml. of fuming nitric acid (sp. gr. 1.5) and 10 ml. of sulfuric acid (sp. gr. 1.84) at 0° for thirty minutes and the mixture was allowed to come to room temperature during one hour. After pouring the solution onto ice, the acid was almost neutralized with potassium hydroxide, and completely neutralized with potassium carbonate. The nitroquinazoline which separated on chilling was recrystallized from alcohol to yield 1.5 g. (56%) of pale yellow needles melting at 174.5–175°.

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[4] We are indebted to Dr. E. K. Marshall, Jr., of Johns Hopkins University and Dr. Arthur P. Richardson of the Squibb Institute for Medical Research for permission to include the results of their screening tests in this paper.

Anal. Calc'd for $C_8H_5N_3O_2$: C, 54.9; H, 2.9.
Found: C, 55.1; H, 3.0.

6-Aminoquinazoline (XXII). (a) *From 4-chloro-6-nitroquinazoline.* One gram of 4-chloro-6-nitroquinazoline was reduced in methanol and the dihydro derivative was dehydogenated as in the preceding cases. Chloroform extraction yielded 57% of 6-aminoquinazoline as bright yellow needles which melted at 213.5–214° after sublimation at 150° and 0.1 mm. and recrystallization of the sublimate from water, alcohol, or benzene.

Anal. Calc'd for $C_8H_7N_3$: C, 66.2; H, 4.9.
Found: C, 66.3; H, 4.8.

(b) *From 6-nitroquinazoline.* To 1 g. of 6-nitroquinazoline in 25 ml. of 6 *N* hydrochloric acid at 0° was added with stirring a solution of 5 g. of stannous chloride in 5 ml. of hydrochloric acid (sp. gr. 1.19). The mixture was stirred for an additional ten minutes and then made strongly alkaline with potassium hydroxide and extracted with ether. From the ether extracts 85% of 6-aminoquinazoline melting at 213–214° after recrystallization from alcohol or benzene was obtained. The melting point of a mixture of this material with that prepared as above was not depressed.

6-Methoxy-4,8-quinazolyl-bis(phenyl sulfide) (XXIV). One gram of pure 4-chloro-6-methoxy-8-nitroquinazoline was added slowly and with stirring to a solution of 5 g. of thiophenol and 0.2 g. of sodium in 25 ml. of absolute methanol. Separation of sodium chloride began immediately, and after ten minutes the mixture was heated to boiling, cooled, and poured into an excess of dilute alkali. After stirring to dissolve the excess thiophenol, the insoluble material was collected and recrystallized from benzene, yielding 1 g. of large colorless prisms which melted at 186–187°. The analytical figures corresponded with those for a *bis*-phenylquinazolyl sulfide with loss of the nitro group rather than with those for the expected 6-methoxy-8-nitro-4-quinazolylphenyl sulfide.

Anal. Calc'd for $C_{15}H_{11}N_3O_3S$: C, 57.5; H, 3.5; N, 13.4; S, 10.2.
Calc'd for $C_{21}H_{16}N_2OS_2$: C, 67.0; H, 4.3; N, 7.4; S, 17.0.
Found: C, 67.1, 67.0; H, 4.4., 4.5; N, 7.3; S, 17.4.

6-Methoxy-8-(4-quinazolonyl)phenyl sulfide (XXVI). The phenyl sulfide group in the 4-position of the above compound was readily selectively removed either by mild acid or alkaline hydrolysis.

(a) A solution of 0.5 g. of the disulfide in 10 ml. of glacial acetic acid and 4 ml. of water was heated at 90° for two hours, during which thiophenol was liberated. After pouring into water, the precipitate was found to consist of a mixture of two compounds. By fractional crystallization from dilute pyridine 0.26 g. (52%) of the original disulfide was recovered as the less soluble component. From the mother liquors 0.14 g. (37%) of the quinazolonylphenyl sulfide was isolated. It formed a felty mass of fine white needles which were soluble in sodium hydroxide solution and melted at 260–261°.

Anal. Calc'd for $C_{15}H_{12}N_2O_2S$: C, 63.4; H, 4.3.
Found: C, 63.4; H, 4.6.

(b) A solution of 0.5 g. of the disulfide in 10 ml. of pyridine containing 2 ml. of water and 1 drop of 40% sodium hydroxide solution was heated at 100° for six hours. On dilution and cooling, 66% yield of the quinazolonylphenyl sulfide was obtained.

(c) A solution of 0.5 g. of the disulfide in 10 ml. of acetic acid containing 2 ml. of water and 1 ml. of hydrochloric acid (sp. gr. 1.19) was heated at 100° for twelve hours. On dilution, 82% yield of the quinazolonylphenyl sulfide was obtained.

6-Methoxy-8-(4-quinazolonyl)phenyl sulfone (XXV). A solution of 0.35 g. of 6-methoxy-8-(4-quinazolonyl)phenyl sulfide and 2 ml. of 30% hydrogen peroxide in 10 ml. of glacial acetic acid was heated at 90° for two hours and then poured into water. The crude sulfone was collected and recrystallized from dilute acetic acid yielding 80% of fine colorless needles which melted at 301-303° (dec., uncorr.) (copper block).

Anal. Calc'd for $C_{15}H_{12}N_2O_4S$: C, 56.9; H, 3.8; N, 8.9; S, 10.1.
Found: C, 56.6; H, 4.1; N, 9.0; S, 10.4.

The ultraviolet absorption spectra were taken on a Beckman quartz spectrophotometer, Model DU. A constant band width of 10Å was used. The solvent in all cases was pure ethanol. The curves thus obtained are shown in Figure 4.

The potentiometric titration data were obtained by dissolving 1 millimole of the substance to be titrated in 50 ml. of 50% alcohol at 27° and titrating this solution with standard 0.1 *N* hydrochloric acid. The *p*H was followed with a Beckman *p*H meter. The *p*H measured is plotted against equivalents of acid added in Figure 5. In the calculation of the dissociation constants, K_b, the equation

$$K_b = \frac{K_{H_2O}}{[H^+]} \times \frac{\frac{c}{2} - [H^+]}{\frac{c}{2} + [H^+]}$$

was used where K_{H_2O} is the dissociation constant of water at 27°, c is the initial concentration of base, and $[H^+]$ is the hydrogen ion concentration at the calculated half-neutralization point. When the value of $[H^+]$ is negligible as compared to $\frac{c}{2}$, as in the case of the stronger bases ($K_b > 10^{-10}$) the simpler equation, $K_b = \frac{K_{H_2O}}{[H^+]}$, was used. No correction was made for the presence of alcohol in the solutions The values of the ionization constants thus obtained are shown in Table I.

The microanalyses here reported were done by Miss Lois May and Mr. William Sashek. The counter-current analysis was done by Mrs. Ann D. Holley.

SUMMARY

1. A practical synthesis for *bz*-substituted quinazolines through the corresponding 4-chloroquinazolines has been developed.

2. The course of catalytic reduction of various quinazoline derivatives has been shown to be primarily dependent on the solvent used.

3. Ultraviolet absorption data and pK_b values have been determined for a number of quinazoline derivatives.

4. Representative potential antimalarial drugs analogous to the 8-aminoquinolines have been prepared in the quinazoline series. The drugs thus prepared were relatively inactive against avian malaria.

5. Quinazoline has been shown to nitrate in the 6-position.

6. An unusual displacement of an aromatic nitro group in 4-chloro-6-methoxy-8-nitroquinazoline in reaction with sodium thiophenoxide has been noted.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CELANESE CORPORATION OF AMERICA]

PREPARATION OF METHYL ISOPROPENYL KETONE FROM METHYL ETHYL KETONE AND FORMALDEHYDE

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The preparation and properties of various vinyl ketones was reviewed by Morgan, Megson, and Pepper in 1938 (1). One of the methods which has been extensively investigated involves an aldol condensation of acetone or methyl ethyl ketone with formaldehyde followed by dehydration of the keto alcohol to the vinyl ketone (1, 2, 3, 4, 5, 6, 7, 8). The factors influencing the condensation of acetone and formaldehyde have been studied in some detail by White and Howard (6); however, a similar investigation has not been reported in the case of methyl ethyl ketone and formaldehyde.

Except for the reported vapor-phase preparation of methyl isopropenyl ketone (9), this compound has been prepared almost exclusively by dehydration of 2-methyl-3-ketobutanol, obtained by an aldol condensation of methyl ethyl ketone and formaldehyde.

$$CH_3COCH_2CH_3 + HCHO \rightarrow HOCH_2CH(CH_3)COCH_3 \xrightarrow{-H_2O} CH_2{=}C(CH_3)COCH_3$$

In view of conflicting information regarding the yields obtained in this reaction, an evaluation of some of the factors involved has been made. The following factors have been investigated:

(I) Mole Ratio of Reactants.
(II) Catalysts and Catalyst Concentration.
(III) Temperature.
(IV) Diluents.

The condensation, unless otherwise specified, was conducted under anhydrous conditions, using paraformaldehyde and freshly distilled neutral methyl ethyl ketone. The crude aldol thus formed was dehydrated with 85% phosphoric acid.

A series of condensations were performed in which the temperature (40–45°) and the catalyst concentration (1.35 meq. KOH/mole formaldehyde) was kept constant. The mole ratio of methyl ethyl ketone to formaldehyde was varied between 3:1 to 30:1. The results are summarized in Table I.

These results indicate that the greater the excess of methyl ethyl ketone the higher the yield of the desired product. Also the rate of reaction was directly proportional to the mole ratio of reactants, as would be expected from a bimolecular reaction. Analogous results have been found by Dreyfus and Drewitt (2) in the case of 3-ketobutanol formed from acetone and formaldehyde.

The work of White (7, 10) stresses the importance of the *p*H of the reaction solution in the condensation of the methyl ethyl ketone and formaldehyde. This investigator recommended an initial *p*H of 7–9, preferably 8.5, for maximum yield; however, since the reaction is carried out in a non-aqueous medium we found the measurement of *p*H impractical. White did not report his method of measurement and we found that the use of a Beckman *p*H meter or of indicator papers was not satisfactory. In view of this difficulty, the effect of alkali catalyst was studied by addition of measured quantities of the alkaline catalyst, expressed in milli-equivalents of KOH/mole of paraformaldehyde.

TABLE I

EFFECT OF MOLE RATIO

MOLE RATIO MEK:HCHO	TIME OF[a] DEPOLYMERIZATION, MIN.	TIME TO[b] COMPLETE CONDENSATION, MIN.	YIELD[c] CRUDE ALDOL, G.	YIELD OF MIK,[d] %
3:1	9	95	75.5	42
5:1	7	37	83.8	54
10:1	4	12	88.2	58
20:1	2	5	93	71
30:1	1–2	3	93	65

Temp. 40–45° Catalyst: alcoholic KOH 1.35 meq/mole HCHO.

[a] Time of depolymerization: represents the time required for the paraformaldehyde to be depolymerized as indicated by clearing of solution.

[b] Negative Tollens test indicating absence of formaldehyde.

[c] Based on 1 mole (30 g.) paraformaldehyde. Theoretical 102 g.

[d] MIK = Methyl isopropenyl ketone, yield based on formaldehyde.

TABLE II

EFFECT OF CATALYST CONCENTRATION, ALCOHOLIC KOH[a]

CONC., MEQ.	TIME OF DEPOLYMERIZATION, MIN.	TIME TO COMPL. COND , MIN.	YIELD OF CRUDE ALDOL, G.	% YIELD MIK
4.7	2	30	94.4	59
3.6	3	20	—	53
2.5	4	22	85.9	55
2.0	4 5	29	80	51
1.5	7	37	83.8	54
1.0	13	43	84.5	59
0.67	31	129	86	55

Temp. 40–55° Mole Ratio M.E.K.:HCHO (5:1)

[a] KOH added as a 0.5 *N* alcoholic solution; according to White 4 ml. of 0.5 *N* KOH is necessary to reach the recommended *p*H of 8.5.

In the experiments listed in Table II, a constant mole ratio of M.E.K.:HCHO (5:1) was used and the temperature was kept at 45°.

From these results, it is apparent that over a range of 0.67 to 4.7 meq. KOH the yield is not materially affected by the alkali concentration. The chief effect of increased catalyst concentration is to increase the rate of the reaction.

The catalytic action of several inorganic salts (Na_2CO_3; $Na_2CO_3 \cdot 10H_2O$; MgO; ZnO) was also investigated. These salts, when added in the solid state to the reaction solution, were found ineffective as catalysts.

A few experiments were conducted at different temperatures in order to evaluate the effect of this factor on the yield of condensation product. The results are summarized in Table III.

Thus, the higher the reaction temperature, the faster the reaction rate; however, high reaction temperatures cause a slight diminution of yield.

In view of the large excess of methyl ethyl ketone necessary to achieve a satisfactory yield, an attempt was made to determine whether the excess served merely as a diluent for the reaction or was required to diminish secondary or side reactions. Condensations were carried out using water and methanol as diluents for the reaction. In both experiments, a low yield of isopropenyl ketone was obtained.

TABLE III

EFFECT OF TEMPERATURE

TEMPERATURE, °C.	TIME OF DEPOLYMERIZATION, MIN.	TIME TO COMPLETE CONDENSATION, MIN.	YIELD OF CRUDE ALDOL, G.	% YIELD MIK
Reflux (80–85)	1	5	76	44
40–45	7	37	83.8	54
0–15	8 hrs.	17 hrs.	82.5	56

EXPERIMENTAL

General procedure. A suspension of paraformaldehyde in anhydrous methyl ethyl ketone was heated to the desired temperature while being stirred efficiently. The catalyst was added and the reaction allowed to proceed until all the formaldehyde was condensed as indicated by a negative test with Tollens reagent. The reaction solution was then neutralized with a dilute solution of acetic acid in methyl ethyl ketone and the excess methyl ethyl ketone removed by distillation. The residue, consisting of 2-methyl-3-ketobutanol and other aldols (1), was dehydrated with phosphoric acid (sp.g. 1.87) at 120–130° under a nitrogen atmosphere. The distillate obtained from this dehydration, consisting of methyl isopropenyl ketone and water, was dried and redistilled. The percentage yields in all cases is based on paraformaldehyde. The efficiency of phosphoric acid as the dehydrating agent is approximately 85%; the same dehydration conditions were employed in all runs.

Water as diluent. A solution of 79 g. (1.1 moles) of methyl ethyl ketone, 500 ml. of water, and 20 ml. $N/10$ KOH was cooled to 5°. Eighty ml. of 38% formalin solution (1 mole) was added and the homogeneous solution was kept at 5° until a negative Tollens test was obtained (5 days); an additional 15 ml. $N/10$ KOH was added during this period. The reaction was neutralized and worked up in the usual manner. Yield of crude aldols 63 g. Yield of methyl isopropenyl ketone 18.3 g. (22%).

Methanol as diluent. A solution of 79 g. (1.1 moles) of methyl ethyl ketone, 500 ml. of methanol and 2 ml. of 0.5 N alcoholic KOH was warmed to 35°. Paraformaldehyde was added in 3-g. portions to the reaction mixture. Time was allowed for each portion of paraformaldehyde to depolymerize before making the next addition. After 15 g. of paraformaldehyde had been added, 2 ml. of 0.5 N alcoholic KOH was again added. An additional 15 g. of paraformaldehyde was then added in similar manner as above. Total 30 g. paraformaldehyde (1 mole), addition time 2 hrs. After standing at 30° for 24 hrs., the reaction was neutralized and worked up in the usual manner. Crude aldol 42 g., methyl isopropenyl ketone 13 g. (16%).

Recommended laboratory procedure for the preparation of methyl isopropenyl ketone. As a result of the foregoing experiments the following is a procedure recommended for the laboratory preparation of methyl isopropenyl ketone from paraformaldehyde and methyl ethyl ketone.

Methyl ethyl ketone (350 g., 5 moles) and paraformaldehyde (1 mole) are mixed in a 3-necked flask equipped with stirrer, reflux, and thermometer. The cloudy reaction mixture is heated to 40° and 3.5 ml. of 0.5 *N* alcoholic KOH is added. The solution is efficiently stirred and kept at 40–45°. During this period the reaction solution clears as a result of depolymerization of the paraformaldehyde. At the end of 30–40 min. the reaction is completed (negative test for formaldehyde with Tollens reagent). The slight excess of alkali is then neutralized with 1 ml. of 2 *N* acetic acid in methyl ethyl ketone. Excess methyl ethyl ketone is removed by distillation. The residue, crude 2-methyl-3-ketobutanol (80–90 g.) is treated with 5 ml. of conc'd phosphoric acid (sp.g. 1.87), 0.5 g. of copper powder, and 0.5 g. of hydroquinone in order to prevent polymerization, and heated at 120–130° in a stream of nitrogen gas. The vapors of methyl isopropenyl ketone and water which are evolved are condensed and separated. The ketone is dried over magnesium sulfate and vacuum distilled. Yield 40–47 g. of methyl isopropenyl ketone; 47–55%, based on paraformaldehyde; b.p. 59–60°/200 mm.; 36–37°/100 mm.; 96–97°/760 mm.; $n_D^{25°}$ 1.4170–1.4210; d_{25}^{25} 0.848–0.852.

Note. A detailed study of the physical constants has been made by Brant (9a). The product as prepared above was of sufficient purity for polymerization experiments.

SUMMARY

1. A study has been made of some of the factors affecting the condensation of methyl ethyl ketone and formaldehyde and the subsequent conversion of the aldol to methyl isopropenyl ketone.

2. The yield of condensation product was found to be directly proportional to the excess of methyl ethyl ketone employed.

3. Concentration of alkaline catalyst and temperature had little effect on the final yield. However, both of these factors affect the rate of the reaction.

4. A method for the preparation of methyl isopropenyl ketone in an over-all yield of 50% is described.

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[FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

THE HALOGENATION OF ARYLOXYACETIC ACIDS AND THEIR HOMOLOGS

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Halogenated aryloxyacetic acids recently have attracted considerable interest as plant hormones and selective weed-killers (1, 9). The preparation usually has been carried out by condensation of chloro- or bromo-acetic acid with the appropriate halogenated phenol or naphthol, but an alternative route is open in the halogenation of phenoxy- and naphthoxy-acetic acids or their functional derivatives. The present paper deals with the latter reaction, which frequently has the advantage that it is less violent and more easily controlled than the halogenation of free phenols; one can obtain well-defined products of desired halogen content by varying the temperature of reaction. Furthermore, the blocking of the free phenolic hydroxyl before the halogenation sometimes permits the introduction of halogen in positions other than those occupied in the free phenol. Similar observations have been recorded for certain substitution reactions in the 1-naphthol series (2, 3, 4).[1]

Several instances of halogenation of phenyloxyacetic acid are known. Ethyl phenoxyacetate has been brominated in the 4-position by Auwers and Hayman (5), the free acid chlorinated by means of sulfuryl chloride by Peratoner (6) and with phosphorus pentachloride by Michael (7), and the phenyl ester brominated by Vandervelde (8).

The present results show that phenoxyacetic acid is chlorinated and brominated first in the 4- and then in the 2-position; monohalogenation proceeds at room temperature, dihalogenation at 60–80°. The sodium salt, the ethyl ester, and the amide all give the 4-chloro compound at room temperature and the 2,4-dichloro derivative at 60–80°. An excess of chlorine at 80° gives finally 2,4,6-trichlorophenoxyacetic acid. (Pentachlorophenoxyacetic acid could only be obtained from pentachlorophenol.) α- and β-Phenoxypropionic acid are equally well para-chlorinated at low temperature, and α-(2,4-dichlorophenoxy)-propionic and -butyric acid are obtained at 30°. As expected, diphenoxyacetic acid gives bis-(2,4-dichlorophenoxy)acetic acid, which has also been synthesized from 2,4-dichlorophenol and dichloroacetic acid.

1-Naphthoxyacetic acid gives at room temperature the 4-chloro derivative, identical with the condensation product of 4-chloro-1-naphthol and bromoacetic acid and different from the product formed from 2-chloro-1-naphthol and bromoacetic acid. Further chlorination of 1-naphthoxyacetic acid at 60° gives the 2,4-dichloro derivative, the constitution of which was established by condensation of 2,4-dichloro-1-naphthol with ethyl bromoacetate and subsequent hydrolysis. Bromination proceeds analogously. 2-Naphthoxyacetic acid is monochlorinated best at 40°, dichlorinated at 60°. The two halogen atoms enter presumably the 1- and 6-positions, respectively.

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[1] In unpublished experiments from our Institute, it has been observed that 1,5-dimethoxynaphthalene is brominated in carbon tetrachloride solution at 4 and 8, while 5-methoxy-1-naphthol in the same solvent gives the 2,8-derivative, and in benzene gives also the 2,6-dibromo isomer.

A third series of halogenations was carried out with the cresoxyacetic acids. 4-Methylphenoxyacetic acid is chlorinated and brominated in the 2-position, the methyl having a weaker *o*-directing influence than the (etherified) hydroxyl group. The chlorinated product has been prepared before by Synerholm and Zimmermann (9) from 2-chloro-4-methylphenol, and the structure of the bromo compound follows from its non-identity with the 3-bromo-4-methylphenoxyacetic acid, obtained from 3-bromo-4-methylphenol and ethyl bromoacetate (with subsequent hydrolysis). The direction of the halogenation is, therefore, identical with that prevailing in the halogenation of *p*-cresol.

2-Methylphenoxyacetic acid has been converted into a mono-, a di-, and a tri-chloro derivative; judging from the well-known behavior of *o*-cresol, one would expect the positions 4, 6, and 3 (or 5) to be the most likely sites of substitution. The first attack, in any event, does not involve position 4, since the monochloro derivative obtained by us (m.p. 131°) is different from the 4-chloro-2-methylphenoxyacetic acid (m.p. 119–120°) prepared by Synerholm and Zimmermann (9) from the respective 4-chloro-2-methylphenol.[2] The halogenation seems, therefore, to deviate from the course it takes in the case of the free *o*-cresol.

EXPERIMENTAL

As an example, the preparation of *4-chlorophenoxyacetic acid* is described.

A. A solution of 15.2 g. of phenoxyacetic acid (10) in 60 cc. of glacial acetic acid containing a trace of iodine was chlorinated with 7.1 g. of gaseous chlorine at room temperature. The product that separated was crystallized from water; m.p. 156°; yield 76% (6, 7, 11).

B. A solution of 15.2 g. of phenoxyacetic acid and 8 g. of sodium hydroxide in 150 cc. of water was cooled and treated with 7.1 g. of chlorine. The crystals were filtered and recrystallized from water; m.p. 156°; yield, 50% (12).

The other halogenation experiments are summarized in Table I.

2,4-Dichlorophenoxyacetic acid from 2,4-dichlorophenol(22),14). *Ethyl 2,4-dichlorophenoxyacetate.* To a solution of 4.6 g. of sodium and 33 g. of 2,4-dichlorophenol in 100 cc. of butyl alcohol, 51 g. of ethyl chloroacetate was added at 25°. The mixture was heated for 2 hours on the water-bath, cooled, and diluted with water. The oil which separated was dried and fractionated; it boiled at 128°/0.2 mm; yield 45 g., 90% n_D^{18} 1.5282.

Anal. Calc'd for $C_{10}H_{10}Cl_2O_3$: C, 48.1; H, 4.0.
Found: C, 47.9; H, 4.2.

Hydrolysis. Ten grams of the ester was heated for 3 hours at 100° with a solution of 2 g. of sodium hydroxide in 20 cc. of water. Upon cooling, the sodium salt separated; it crystallized from alcohol in needles of m.p. 215°. The acid formed white crystals; it boiled at 160°/0.4 mm. and had m.p. 141°; yield 8 g.

Anal. Calc'd for $C_8H_6Cl_2O_3$: C, 43.9; H, 2.6.
Found: C, 43.7; H, 2.6.

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[2] Dr. Synerholm has kindly put at our disposal a sample of his product, which depresses the melting point of the above-described monochloro-2-methylphenoxyacetic acid. His preparations of 2,4,6-trichlorophenoxyacetic acid, of 2-chloro-4-methylphenoxyacetic acid, and of 2-bromo-4-methylphenoxyacetic acid have been found identical with the corresponding products prepared as described above. (Note added February 13, 1947).

TABLE I

ARYLOXYACETIC ACID DERIVATIVES

STARTING MATERIAL	G.	CC. AcOH	CATALYST	HALOGEN, G.	TEMP. °C.	PRODUCT	M.P. °C	YIELD, %	NEUTR. EQUIV.		REMARKS
									Calc'd	Found [b]	
Ethyl phenoxyacetate (13)	90	50	Iodine	Cl_2, 35.5	20	Ethyl 4-chlorophenoxyacetate	48[a]	80			[c]
Phenoxyacetamide (13)	6.8	10	Iron	Cl_2, 3.6	20	4-Chlorophenoxyacetamide	140[d]				
Phenoxyacetic acid	152	300	Iron	Cl_2, 142.0	20, then 60	2,4-Dichlorophenoxyacetic acid	141[e]	82			
Phenoxyacetamide	6.8	20	Iron	Cl_2, 7.2	40	2,4-Dichlorophenoxyacetamide	130[f]			[g]	
Phenoxyacetic acid	15.2	60	Iron	Cl_2, 21.3	80	2,4,6-Trichlorophenoxyacetic acid	177[h]	65	255	253	
Phenoxyacetic acid	15.2	60	Iodine	Br_2, 16.0	20	4-Bromophenoxyacetic acid	154[i] (5)	80	231	230	
Phenoxyacetic acid	15.2	100	Iodine	Br_2, 32.0	20, then 60	2,4-Dibromophenoxyacetic acid	152[k]	74	310	308	[l]
Ethyl α-phenoxypropionate (16)	19.4	25	Iodine	Cl_2, 7.1	20	Ethyl α-(4-chlorophenoxy)propionate	b.p. 130/0.7 mm.	70			[m]
α-Phenoxypropionic acid (15)	16.6	40	Iodine	Cl_2, 7.1	0	α-(4-Chlorophenoxy)propionic acid	66[n]	80	200	199	

α-Phenoxypropionic acid	16.6	40	Iodine	Cl_2, 14.2	30	α-(2,4-Dichlorophenoxy)-propionic acid	115[e] (15)	60	235	234	
β-Phenoxypropionic acid (17)	16.6	40	Iodine	Cl_2, 7.1	20	β-(4-Chlorophenoxy)propionic acid	139[p]	68	200	200	
α-Phenoxybutyric acid (16)	2.5	5	Iron		20	α-(2,4-Dichlorophenoxy)-butyric acid	80[q]	68	249	250	
Diphenoxyacetic acid (5)	24.0	100	Iodine	Cl_2, 14.2	50	bis-(2,4-Dichlorophenoxy)acetic acid	152[p]	70	382	382	
1-Naphthoxyacetic acid (18)	10.1	50	Iron	Cl_2. 3 6	20	4-Chloro-1-naphthoxy-acetic acid	169[p]	60	236	235	
1-Naphthoxyacetic acid	20.2	60	Iron	Cl_2, 14.2	60	2,4-Dichloro-1-naphthoxy-acetic acid	178[r]	72	271	271	
1-Naphthoxyacetic acid	10.1	50	Iodine	Br_2, 8.0	20	4-Bromo-1-naphthoxy-acetic acid	167[p]		281	280	
1-Naphthoxyacetic acid	10.1	50	Iodine	Br_2, 16.0	20, then 100	2,4-Dibromo-1-naphthoxy-acetic acid	196.5[p]	80	360	360	
2-Naphthoxyacetic acid (19)	10.1	50	Iron	Cl_2, 3 6	40	1-Chloro-2-naphthoxy-acetic acid	156[k]	70	236	236	
2-Naphthoxyacetic acid	10.1	50	Iron	Cl_2, 7.2	60	1,6-Dichloro-2-naphthoxy-acetic acid (?)	166[i]	62	271	272	
4-Methylphenoxyacetic acid (20)	8.3	50	Iron	Cl_2, 3.6	20	2-Chloro-4-methylphen-oxyacetic acid	140[t]	50	201	201	

TABLE I—*Continued*

STARTING MATERIAL	G.	CC. AcOH	CATALYST	HALOGEN, G.	TEMP. °C.	PRODUCT	M.P., °C	YIELD, %	NEUTR. EQUIV.		RE-MARKS
4-Methylphenoxyacetic acid	8.3	50	Iron	Br_2, 8.0	5	2-Bromo-4-methylphenoxyacetic acid	149[t,u]	83			[v]
2-Methylphenoxyacetic acid (21)	8.3	50	Iodine	Cl_2, 3.6	0	Monochloro derivative	131	60	200	198	
2-Methylphenoxyacetic acid	1.7	15	Iodine	Cl_2, 1.5	20	Dichloro derivative	179[w]	24	235	233	
2-Methylphenoxyacetic acid	8.3	50	—	Cl_2, 10.7	60	Trichloro derivative	174[k,x]	75	270	270	[y]

[a] B.p. 180°/22 mm. [b] *Anal.* Calc'd for $C_{10}H_{11}O_2Cl$: C, 55.8; H, 5.1. Found: C, 55.4; H, 5.0. [c] Hydrolysis of 21.5 g. in 20 cc. of alcohol with 4 g. of sodium hydroxide in 20 cc. of water gave the acid; from 50% acetic acid, m.p. 156°; yield 80%. [d] Literature (11a): 133°. [e] Literature (14): 138°. [f] Needles from alcohol or benzene. [g] *Anal.* Calc'd for $C_8H_7Cl_2NO_2$: N, 6.3. Found: N, 6.4. [h] Literature (9, 15): 190°. [i] From alcohol. [k] Needles from benzene. [l] *Anal.* Calc'd for $C_8H_6Br_2O_3$: C, 39.7; H, 1.9. Found: C, 40.0; H, 2.2. [m] Hydrolysis of 23 g. in 25 cc. of alcohol with 4 g. sodium hydroxide in 15 cc. of water gave the acid, from benzene, m.p. 66°; yield 85%. [n] Purified by vacuum distillation; from benzene. [o] From dilute alcohol. [p] From benzene. [q] B.p. 145–150°/0.2 mm; trituration with petroleum ether. [r] Purification by distillation *in vacuo*; b.p. 220–230°/0.8 mm. From benzene, needles. [s] The sodium salt, shiny leaflets, is only sparingly soluble in water. *Anal.* Calc'd for $C_{12}H_8Br_2O_3$: C, 40.0; H, 2.2. Found: C, 40.0; H, 2 2. [t] Silky needles from water. [u] Literature (9): m.p. 145°. [v] *Anal.* Calc'd for $C_9H_9BrO_3$: C, 44.0; H, 3.6. Found: C, 44.0; H, 3.8. [w] From acetic acid. [x] Strong m.p. depression with the dichloro derivative. [y] *Anal.* Calc'd for $C_9H_7Cl_3O_3$: C, 40.0; H, 2.6. Found: C, 40.1; H, 2.5.

Pentachlorophenoxyacetic acid. Ethyl pentachlorophenoxyacetate. To a solution of 1.2 g. of sodium in 50 cc. of absolute alcohol, 13.3 g. of pentachlorophenol (23) and 8.4 g. of ethyl bromoacetate were added in succession. The mixture was heated on the water-bath for one hour. The precipitate which appeared upon cooling, was collected, washed with water and recrystallized first from alcohol, then from petroleum ether. The ester formed needles of m.p. 110–111°; yield 14 g., 80%.

Anal. Calc'd for $C_{10}H_7Cl_5O_3$: C, 34.1; H, 2.0.
Found: C, 34.5; H, 2.5.

Hydrolysis with 10% alcoholic potassium hydroxide solution gave the free acid which crystallized nicely from toluene. It melted at 195–196.°

Anal. Calc'd for $C_8H_3Cl_5O_3$: Neutr. equiv., 324.
Found: Neutr. equiv., 322.5.

bis-(2,4-Dichlorophenoxy)acetic acid. To a solution of 12.5 g. of sodium in 150 cc. of butyl alcohol, 41 g. of 2,4-dichlorophenol and 33 g. of dichloroacetic acid were added in succession. The mixture was heated for three hours on the water-bath. The acid proved very soluble in alcohol and acetone, but crystallized well from benzene; yield 52%. It melted at 152° and did not depress the m.p. of the dichlorophenoxyacetic acid, prepared by chlorination of phenoxyacetic acid.

4-Chloro-1-naphthoxyacetic acid. The solutions made from 7 g. of bromoacetic acid and 4.3 g. of sodium bicarbonate in 10 cc. of water, and from 9 g. of 4-chloro-1-naphthol (24) and 2 g. of sodium hydroxide in 10 cc. of water, respectively, were mixed and the mixture was heated at 100° for four hours. The solid which separated was brought into solution by addition of 250 cc. of water, and the solution was treated with charcoal, filtered, and acidified with 5% hydrochloric acid. The acid was recrystallized from benzene, it melted at 169° and proved identical with the acid prepared from 1-naphthoxyacetic acid and chlorine. The yield was 64%.

2-Chloro-1-naphthoxyacetic acid. A solution of 0.6 g. of sodium, 4.5 g. of 2-chloro-1-naphthol (24a), and 4.1 g. of sodium bromoacetate in 20 cc. of alcohol was heated for four hours on the water-bath. The alcohol was evaporated and the residue dissolved in water and, after extraction with ether, acidified with 5% hydrochloric acid. After recrystallization from benzene, the acid had m.p. 134°; yield, 74%.

Anal. Calc'd for $C_{12}H_9ClO_3$: Neutr. equiv., 236. Found: Neutr. equiv., 234.5; 235.

2,4-Dichloro-1-naphthoxyacetic acid. To a solution of 2.3 g. of sodium in 75 cc. of alcohol, 21.5 g. of 2,4-dichloro-1-naphthol (25) in 75 cc. of alcohol and 16.8 g. of ethyl bromoacetate were added in succession. After one hour on the steam-bath, the mixture was cooled and the solid filtered and recrystallized from petroleum ether. The *ethyl ester* had m.p. 71°; b.p. 165°/0.05 mm; yield 90%.

Anal. Calc'd for $C_{14}H_{12}Cl_2O_3$: C, 56.0; H, 4.0; Cl, 23.7.
Found: C, 56.3; H, 4.4; Cl, 23.9.

Hydrolysis gave the free acid, m.p. 178°, in 80% yield. It was identical with the product obtained by dichlorination of 1-naphthoxyacetic acid.

2,4-Dibromo-1-naphthol (26) could not be condensed with ethyl bromoacetate, as sodium alkoxide and even acetate convert it into an indigo-blue substance (27).

6-Bromo-2-naphthoxyacetic acid. To a cold solution of 2.3 g. of sodium in 75 cc. of absolute alcohol, 22.3 g. of 6-bromo-2-naphthol (28) and 16.8 g. of ethyl bromoacetate were added in succession. After one hour on the water-bath, the difficultly soluble potassium salt of the desired acid was precipitated by addition of a concentrated aqueous solution of 14 g. of potassium hydroxide. The solution of the salt in boiling water was acidified. The acid had m.p. 210°; yield 88%.

Anal. Calc'd for $C_{12}H_9BrO_3$: Neutr. equiv., 281. Found: Neutr. equiv., 280.

1,6-Dibromo-2-naphthoxyacetic acid. To a solution of 1.2 g. of sodium in 50 cc. of alcohol, 15.1 g. of 1,6-dibromo-2-napthol (28) and 8.4 g. of ethyl bromoacetate were added in succession. The crude ester obtained was hydrolyzed with alcoholic potassium hydroxide solution and the acid isolated in 85% yield. After recrystallization from toluene, it melted at 178°.

Anal. Calc'd for $C_{12}H_8Br_2O_3$: Neutr. equiv., 360. Found: Neutr. equiv., 360.

3-Bromo-4-methylphenoxyacetic acid. To a solution of sodium ethoxide, prepared from 2.3 g. of sodium in 75 cc. of alcohol, 18.7 g. of 3-bromo-4-methylphenol (29) (b.p. 218–219°) and 16.7 g. of ethyl bromoacetate were added in succession at 0°. Within one hour, the mixture was gradually brought up to boiling temperature and, after addition of 65 cc. of 10% sodium hydroxide solution, was kept for ten more minutes on the steam-bath. The solution of the sodium salt was treated with charcoal, filtered and acidified; yield 85%; m.p. 145°.

Anal. Calc'd for $C_9H_9BrO_3$: Neutr. equiv., 245. Found: Neutr. equiv., 243.

This product gave a strong depression of the melting point, when mixed with the acid formed in the direct bromination of 4-methylphenoxyacetic acid.

SUMMARY

Aryloxy-fatty acids and their esters and amides are easily chlorinated and brominated step by step.

The following substances have been investigated: phenoxyacetic acid and its ethyl ester and amide; α- and β-phenoxypropionic acid; ethyl α-phenoxypropionate; α-phenoxybutyric acid; diphenoxyacetic acid; 1- and 2-naphthoxyacetic acid; (4-methylphenoxy)acetic acid and (2-methylphenoxy)acetic acid.

Thirty-two halogenated derivatives have been synthesized either by this method or by the usual condensation of halogenated phenols with halogeno-fatty acids.

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[From the Daniel Sieff Research Institute]

DERIVATIVES OF 6-NITRO- AND 6-AMINO-QUINOLINE

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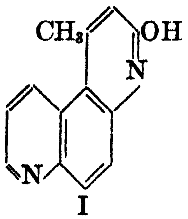
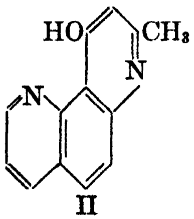
In the recent investigations of aminoquinoline derivatives as chemotherapeutic agents, little attention has been given to 6-aminoquinoline derivatives, although one of them, the methosulfate of the *sym.*-di-(6-quinolyl)urea (Acaprine) has been used successfully in veterinary medicine (1). The present paper describes further experiments in this series. The preparation of 6-nitroquinoline by the Skraup synthesis proceeds satisfactorily (70% yield) if one starts with *p*-nitroacetanilide and not with *p*-nitroaniline. This modification of the Skraup synthesis, discovered by Manske, Leger, and Gallagher (2) and recently used in a number of quinoline syntheses,[1] decreases the usual violence of the reaction and the formation of tarry by-products.[2]

6-Aminoquinoline is obtained by catalytic reduction of the 6-nitro compound in almost quantitative yield (4); an alternative method used successfully in the case of 3-bromoquinoline by Kuhn and Westphal (5), is the reaction of 6-bromoquinoline with ammonia in the presence of cupric oxide (85% yield). *sym.*-Di-(6-quinolyl)urea can be obtained from the amino compound not only with phosgene (1), but more conveniently with urea; a mono- and a di-methosulfate have been prepared. Thiourea gives analogously *sym.*-di-(6-quinolyl)thiourea, previously (1) obtained by means of carbon disulfide or thiophosgene.

The condensation of 6-aminoquinoline with ethyl acetoacetate and cyclization of the acetoaceto-6-quinolylamide formed gave a substance regarded as 2-hydroxy-4-methyl-5,6,3′,2′-pyridinoquinoline (I), an isomer of the compound II, prepared by Kermack and Webster (6) from 6-amino-4-hydroxy-2-methylquinoline by the Skraup synthesis.



I



II

EXPERIMENTAL

6-Nitroquinoline. A 5-liter flask equipped with glycerol-sealed stirrer, thermometer, and reflux condenser was charged with 180 g. (1 mole) of *p*-nitroacetanilide, 368.2 g. (4 moles) of glycerol, and 172.4 g. (0.75 mole) of arsenic pentoxide, and 40 g. of concentrated sulfuric acid was added at such a rate that the temperature did not exceed 130° (15–20 minutes). The mixture was heated gently in an oil-bath for 4 hours, cooled to room temperature, and poured into 5 l. of water. The product was then decolorized with 50 g. of Norit at room temperature (1 hour; agitation), filtered, and slowly neutralized with aqueous ammonia. The yield of product, once crystallized from alcohol was 122 g. (70%); m.p. 150°, b.p. 170°/0.2 mm.

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[1] Kaslow and Raymond (3), 4-methoxyacetanilide. Lauer (3), 2-bromo-4-acetamino-5-nitroanisole; 3-nitro-4-acetaminodiphenyl ether. Snyder and Easton (3), 5-acetamido-2-methoxy-4-nitrobiphenyl. Carmack, Kissinger, and Von (3), 3-methyl-4-methoxyacetanilide. Elderfield (3), 4-acetamino-5-nitroveratrole; 2-fluoro-4-acetamino-5-nitroanisole.

[2] The synthesis of the important 6-methoxy-8-nitroquinoline is also simplified by this modification of the classical method (Experimental Part).

6-Aminoquinoline (4). (a) A solution of 16 g. of 6-nitroquinoline in 80 cc. of alcohol was hydrogenated at room temperature and atmospheric pressure in the presence of 0.5 g. of 2% palladium-calcium carbonate catalyst (exothermic reaction). The reaction product crystallized when the filtered solution was freed from the solvent. The amine crystallized from benzene-petroleum ether in lancet-shaped crystals, m.p. 118°; yield 13 g., b.p. 146°/0.3 mm. *Monohydrochloride*, m.p. 109° (from ethanol); *dihydrochloride*, m.p. 250° (insoluble in alcohol); *methochloride*, m.p. 242°.

(b) 6-Bromoquinoline (19.4 g) was heated for 15 hours with 150 cc. of 20% aqueous ammonia solution and 5 g. of freshly precipitated cupric oxide at 140–150° (autoclave); yield 80%.

sym.-Di-(6-quinolyl)urea. 6-Aminoquinoline (2.9 g.) was cautiously heated with urea (0.7 g.) and 30% hydrochloric acid (2 g.) until all the water had evaporated. The mass was then heated slowly to 150–160°, at which point an exothermic reaction set in and the temperature rose to 200–220°. When the reaction was over, the mass was pulverized, dissolved in dilute hydrochloric acid, and the solution was filtered and neutralized with sodium hydroxide. Crystallization from pyridine gave crystals melting at 262°; yield 90%.

Anal. Calc'd for $C_{19}H_{14}N_4O$: C, 72.6; H, 4.5.
Found: C, 72.2; H, 4.6.

Monomethosulfate. When 35 g. of the urea derivative was heated with 12.6 g. of dimethyl sulfate and 150 cc. of methyl alcohol, a clear solution soon resulted, and the quaternary salt began to crystallize; it formed yellow crystals, m.p. 168°.

Anal. Calc'd for $C_{21}H_{20}N_4O_5S$: N, 12.7. Found: N, 12.6.

The *bis-methosulfate* was prepared analogously, with 25.2 g. of dimethyl sulfate; m.p. 237° (decomp.).

Anal. Calc'd for $C_{23}H_{26}N_4O_9S_2$: C, 48.9; H, 9.9.
Found: C, 48.7; H, 10.0.

sym.-Di-(6-quinolyl)thiourea. A mixture of 18 g. of 6-aminoquinoline monohydrochloride and 3.8 g. of thiourea was heated at 160° for 2 hours. The product was triturated with aqueous ammonia and crystallized from acetic acid; m.p. 217° [Lit. (1): 199°].

Anal. Calc'd for $C_{19}H_{14}N_4S$: N, 17.0. Found: N, 17.8.

The *bis-methosulfate*, prepared as above, was recrystallized from dilute alcohol; m.p. 208°.

Anal. Calc'd for $C_{23}H_{26}N_4O_8S_3$: N, 9.6. Found: N, 9.4.

2-Hydroxy-4-methyl-5,6,3',2'-pyridinoquinoline (*I*). To 7.2 g. of molten 6-aminoquinoline, 5.8 g. of ethyl acetoacetate was added at 160°. Within a few seconds, liberation of water set in and after 24 hours the mass solidified. The dry product was added, with stirring, to 120 cc. of paraffin oil heated at 250°, and the mass was kept at this temperature for 30 minutes. The crystalline product was isolated by centrifuging, and recrystallized from alcohol; m.p. 353° (decomp.) (7).

3-Nitro-4-acetanisidide. A solution of 492 g. of *p*-anisidine in 1.6 l. of glacial acetic acid was treated with 500 cc. of acetic anhydride at 20°; then with stirring, a solution of 168 cc. of nitric acid ($d = 1.52$, free of nitrous acid) in 250 cc. of glacial acetic acid was slowly added, the temperature not exceeding 15° (2 hours; the lower end of the dropping-funnel dips into the solution). When $\frac{3}{4}$ of the nitric acid had been added the product began to crystallize. After 4 hours at room temperature, the mixture was filtered and the mother liquor (2.5 l.) used for a second batch. The crystals were washed with hot water, which was also saved; yield, 321 g.; m.p. 117°.

To a solution of 492 g. of *p*-anisidine in the 2.5 l. of mother liquor from the first reaction, 500 cc. of acetic anhydride and 168 cc. of nitric acid (1.52) were added under the same conditions as in the first reaction. The mixture was stirred for 8 hours, and 4 l. water added. The filtered crystals were washed with the (hot) first wash water and then twice with 500 cc. of fresh hot water; total yield: 1450 g. (86%).

6-Methoxy-8-nitroquinoline. In a 5-l. three-necked round-bottomed flask mounted in an oil-bath and fitted with an efficient reflux condenser of wide bore, stirrer, and thermometer, were placed in the order given: 576 g. of arsenic acid, 1,040 g. of glycerol, 1,500 g. of conc'd sulfuric acid, 840 g. of 3-nitro-4-acetanisidide (maximum temperature 75°). The contents of the flask were well mixed and the mixture heated with stirring for 2 hours at 100°, then slowly to 110°. As soon as the liquid began to boil, the oil-bath was removed, since the heat evolved by the reaction is sufficient to keep the mixture boiling for 30 minutes, and to raise the temperature to 140°. If the reaction proceeds too violently at the beginning, the reflux condenser may be assisted by placing a wet towel over the upper part of the flask. When the boiling ceased, heat was again applied and the mixture boiled for 3 hours at 135–140°. (If a 5-cc. portion of the mixture in 20 cc. of water becomes red when made alkaline with ammonia, the reaction is still incomplete.) The mixture was cooled to 80°, diluted with 4 l. of water, and permitted to stand overnight with 20 g. of Norit. A small quantity of a solid impurity was removed by filtration and 4 l. of 33% sodium hydroxide and then 500 cc. of aqueous ammonia were added. The product was collected, washed with water, and dried. The dried product was extracted with benzene, toluene, or dichloroethane (Soxhlet apparatus) and if necessary recrystallized from ethanol; yield 50–55%; m.p. 157–159°.

6-Methoxy-8-aminoquinoline. A suspension of 204 g. of powdered 6-methoxy-8-nitroquinoline in 500 cc. of ethanol was hydrogenated in the presence of 0.2 g. of palladium on barium sulfate (5%) at normal pressure, which takes about six hours. After filtration from the catalyst, the alcohol was distilled and the residue distilled *in vacuo*; b.p. 150°/1 mm.; m.p. 53°; yield 95%.

Rehovoth, Palestine

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[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE [illegible] LTH]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XXI. GUANIDINE AND BIGUANIDE DERIVATIVES OF PHENANTHRENE[1,2]

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With a view to obtaining compounds of possible prophylactic value, antimalarial researches have been extended to include guanidine and biguanide derivatives of phenanthrene (I, II). Several considerations suggested this line of approach to new antimalarials, foremost of which were the high activity shown by phenanthryl-9-alkamines (1) and the reported prophylactic action, in avian malaria, of *p*-chlorophenyl-guanidine and -biguanide derivatives (2, 3).

Phen-9-NHC(:NH)NR_1R_2
I-a $R_1 = R_2 = H$
-b $R_1 = R_2 = C_2H_5$
-c $R_1 = C_2H_5$ or $i\text{-}C_3H_7$, $R_2 = H$
-d R_1 = Phen-9-, $R_2 = H$

Phen-9-NHC(:NH)NHC(:NH)NR_1R_2
II-a $R_1 = R_2 = H$
-b $R_1 = CH_3$ or $i\text{-}C_3H_7$, $R_2 = H$
-c R_1 = Phen-9-, $R_2 = H$

The simplest member (I-a) of the group of compounds described in this paper was obtained by condensing 9-phenanthrylamine hydrochloride with cyanamide. Mono- and di-alkyl derivatives (I-b, I-c) could not be prepared in the same general way but were formed in 50–80% yields from ethyl-, diethyl- and isopropylamine hydrochlorides and 9-phenanthrylcyanamide. The latter was most advantageously synthesized by the metathesis of 9-phenanthrylamine and cyanogen bromide in boiling ethyl acetate or boiling absolute ether, 1,3-di-(9-phenanthryl)guanidine (I-d) being obtained as a by-product. When this reaction was carried out in boiling ethanol, I-d was the predominant product, and no phenanthrylcyanamide could be isolated. Finally, I-d was formed in good yield on refluxing together in ethyl acetate, equimolar amounts of 9-phenanthrylamine hydrochloride and 9-phenanthrylcyanamide.

By the condensation of 9-phenanthrylamine hydrochloride with cyanoguanidine, 9-phenanthrylbiguanide (II-a) resulted in 60% yield. Similarly, 1-methyl- and 1-isopropyl-3-cyanoguanidines led to compounds of the type II-b. The necessary alkyl-cyanoguanidines, hitherto unreported, were obtained by the following series of reactions.

$$\text{RN:C:S} + \text{NaNHCN} \rightarrow \text{RN:C(SNa)NHCN} \xrightarrow{CH_3I} \text{RN:C(SCH}_3\text{)NHCN}$$

$$\xrightarrow[NH_3]{\text{Alcoholic}} \text{RNHC(:NH)NHCN} \qquad (R = CH_3 \text{ or } i\text{-}C_3H_7)$$

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[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] This paper was presented at the American Chemical Society meeting in Atlantic City, New Jersey, in April, 1946. Shortly before it was submitted for publication the paper, "Some Aryl-diguanide Derivatives" (4), came to our attention.

The same synthetic scheme was utilized to prepare 1-cyano-3-(9-phenanthryl)-guanidine (III), a potential intermediate to 1-aryl- or 1-alkyl-, and 1,1-dialkyl-5-(9-phenanthryl)biguanides. The reaction of III with 9-phenanthrylamine hydrochloride did take place readily, in boiling ethanol, to yield II-c, but under the same conditions with methyl-, ethyl-, or diethyl-amine hydrochloride, starting materials were recovered. In boiling amyl alcohol, in the presence of aliphatic amine hydrochlorides, the alkali-soluble III (m.p. 189–190°) was converted to an alkali-insoluble *isomer* (m.p. 213–214°) which separated from the reaction mixture as the hydrochloride. This transformation occurred to a much lesser extent in boiling dioxane and scarcely at all in ethanol at 130°. The structure of the isomeric product has not been determined.

None of the compounds tested[3] showed activity against *gallinaceum* malaria in chicks. The work is being continued to study the role of nuclear halogen and other factors that may have a bearing on activity.

Acknowledgment. The microanalyses were carried out by Mr. Charles A. Kinser of this Laboratory, and Mr. Edward A. Garlock, Jr. I wish to express my appreciation to Dr. Erich Mosettig for suggesting this problem.

EXPERIMENTAL[4]

9-Phenanthrylguanidine hydrochloride (SN 14,836). A mixture of 13 g. of 9-phenanthrylamine hydrochloride (5), 4.0 g. of cyanamide, and 125 cc. of 95% ethanol was refluxed for thirty-five hours. The alcohol was evaporated *in vacuo* and the residue partitioned between dilute aqueous ammonia and ether. After drying (Na_2SO_4) and evaporation of the ether layer, the residual oil was dissolved in 50 cc. of acetone and the solution acidified with 15 cc. of 15% alcoholic HCl. Addition of 25 cc. of ether followed by chilling in ice, precipitated 4.5 g. of 9-phenanthrylamine hydrochloride. Upon dilution of the filtrate with ether the guanidine hydrochloride slowly crystallized; yield 5.2 g., m.p. 250–255°. It crystallized from absolute ethanol-ether in clusters of sharp needles, m.p. 259–260°.

Anal. Calc'd for $C_{15}H_{14}ClN_3$: C, 66.30; H, 5.19.
Found: C, 66.18; H, 5.35.

9-Phenanthrylcyanamide. A mixture of 5.0 g. (2 moles) of 9-phenanthrylamine (5), 1.5 g. (1 mole) of cyanogen bromide, and 25 cc. of ethyl acetate was refluxed for fifty minutes. The amine hydrobromide was collected and the filtrate evaporated to dryness *in vacuo.* The residue was treated with 25 cc. of alcohol and about 100 cc. of 0.5% sodium hydroxide, the mixture heated quickly to boiling, cooled, and filtered. Acidification of the filtrate with acetic acid yielded 1.4 g. of product which crystallized from ethyl acetate in clusters of large needles, m.p. 152–154° (temperature rise 20° per minute). If the m.p. was taken in the usual way, the compound melted (with apparent decomposition) at 140–180°.

Anal. Calc'd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62.
Found: C, 82.87; H, 4.83.

The above preparation could be made equally well in boiling absolute ether (twenty-four hours).

1,3-Di-(9-phenanthryl)guanidine (SN 14,837). This compound was obtained in small yield in the above reaction between cyanogen bromide and 9-phenanthrylamine, and in about 50% yield when ethanol served as the solvent in the exchange. It was isolated from the alkali-insoluble precipitate. It could also be obtained by refluxing together for forty-eight hours equimolar amounts of 9-phenanthrylamine hydrochloride and 9-phenanthrylcyanamide, in ethyl acetate. It crystallized from dioxane-ethanol in white hexagons of m.p. 236–237°.

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[3] The Survey Number, designated SN (see experimental), identifies a drug in the files of the Survey of Antimalarial drugs. Drugs marked with an asterisk were also tested.

[4] All melting points are uncorrected.

Anal. Calc'd for $C_{29}H_{21}N_3$: C, 84.64; H, 5.14.
Found: C, 84.56; H, 5.30.

1-Ethyl-3-(9-phenanthryl)guanidine hydrochloride (SN 14,839). A mixture of 4.0 g. of 9-phenanthrylcyanamide, 1.6 g. of ethylamine hydrochloride, and 40 cc. of ethyl acetate was refluxed for fourteen hours and cooled to 0°. The solvent was decanted from a viscous lower layer and the latter partitioned between ether and an excess of dilute sodium hydroxide. The residue from drying (Na_2SO_4) and evaporation of the ether layer was dissolved in 50 cc. of ethyl acetate and acidified with 4 cc. of 15% alcoholic HCl to yield 4.6 g. of a hydrochloride. It crystallized from absolute ethanol-ethyl acetate in broad needles, m.p. 90–93° to a frothy melt (after drying in a desiccator).

Anal. Calc'd for $C_{17}H_{18}ClN_3 \cdot \frac{1}{2}\ CH_3COOC_2H_5$: C, 66.39; H, 6.45; $CH_3\ COOC_2H_5$, 12.81.
Found: C, 66.63; H, 6.50; loss in wt. (97° at 1 mm.), 12.44.

The picrate, prepared by adding an excess of alcoholic picric acid to a water solution of the hydrochloride, crystallized from 95% ethanol in yellow crusts, m.p. 211–212°.

Anal. Calc'd for $C_{23}H_{20}N_6O_7$: C, 56.10; H, 4.09.
Found: C, 56.09; H, 4.03.

1,1-Diethyl-3-(9-phenanthryl)guanidine hydrochloride (SN 15,050). This compound was prepared like the foregoing one, in a yield of 80%. It crystallized from absolute ethanol-ethyl acetate in heavy prisms, m.p. 97–101° to a frothy melt which became clear at 135°.

Anal. Calc'd for $C_{19}H_{22}ClN_3 \cdot CH_3COOC_2H_5$: C, 66.40; H, 7.27; $CH_3COOC_2H_5$, 21.18.
Found: C, 66.51; H, 7.17; loss in wt. (97° at 1 mm.), 20.03.

The picrate (from 95% ethanol) melted at 208–209.5°; yellow hexagonal prisms.

Anal. Calc'd for $C_{25}H_{24}N_6O_7$: C, 57.77; H, 4.65.
Found: C, 57.80; H 4.75.

1-Isopropyl-3-(9-phenanthryl)guanidine hydrochloride (SN 15,053). As described for the two foregoing analogs, (reflux time 24 hours), this hydrochloride was obtained in about 50% yield. It appeared as clusters of fine crystals of m.p. 232–234°.

Anal. Calc'd for $C_{18}H_{20}ClN_3 \cdot CH_3COOC_2H_5$: C, 65.74; H, 7.02; $CH_3COOC_2H_5$, 21.86.
Found: C, 65.78; H, 6.93; loss in wt. (130° at 1 mm.), 21.72.

The picrate crystallized from aqueous ethanol in clusters of yellow, boat-shaped crystals, m.p. 188–189°.

Anal. Calc'd for $C_{24}H_{22}N_6O_7$: C, 56.90; H, 4.38.
Found: C, 56.82; H, 4.39.

1-(9-Phenanthryl)biguanide hydrochloride (SN 14,022). A mixture of 15 g. of 9-phenanthrylamine hydrochloride, 6 g. of dicyandiamide, and 125 cc. of 95% ethanol was refluxed for 10–15 hours. After cooling in ice, the biguanide derivative was obtained in a yield of 12.5 g., m.p. 238–241°. Two recrystallizations from 90% ethanol gave the m.p. 241–242° (decomp.); curved needles.

Anal. Calc'd for $C_{16}H_{16}ClN_5$: C, 61.25; H, 5.14.
Found: C, 61.64; H, 5.45.

The base crystallized from 70% ethanol in thick, square plates, m.p. 179–180.5°.

Anal. Calc'd for $C_{16}H_{15}N_5$: C, 69.35; H, 5.45.
Found: C, 69.37; H, 5.78.

1-Cyano-3-methylguanidine. 1-Cyano-2,3-dimethyl-2-thiopseudourea (6, 7) (1.0 g.) and 10 cc. of 15% alcoholic ammonia[6] were heated together in a sealed tube for five hours at 95°. Evaporation to dryness *in vacuo* left 0.75 g. of oily 1-cyano-3-methylguanidine which was sufficiently pure for the next reaction. It could be crystallized, in poor yield, from ethyl acetate; prisms, m.p. 91–92°.

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[6] This and subsequent desulfurization procedures were modeled after one used by Wheeler and Jamieson (7) in the preparation of 1-phenyl-3-cyanoguanidine.

Anal. Calc'd for $C_3H_6N_4$: C, 36.70; H, 6.17.
Found: C, 36.86; H, 5.97.

1-Methyl-5-(9-phenanthryl)biguanide hydrochloride (SN 15,080). A mixture of 1.1 g. of the crude, oily 1-methyl-3-cyanoguanidine, 2.5 g. of 9-phenanthrylamine hydrochloride, and 25 cc. of 95% ethanol was refluxed for about fifteen hours and the alcohol evaporated *in vacuo*. The oily residue crystallized from acetone in a yield of 2.1 g., m.p. 213–216°. After two recrystallizations from absolute ethanol-ether the m.p. was 216–217°; slender needles.

Anal. Calc'd for $C_{17}H_{18}ClN_5$: C, 62.29; H, 5.53.
Found: C, 62.47; H, 5.56.

The picrate crystallized from aqueous ethanol in orange rods, m.p. 201–202°.

Anal. Calc'd for $C_{23}H_{20}N_8O_7$: C, 53.07; H, 3.87.
Found: C, 53.18; H, 3.78.

1-Cyano-3-isopropyl-2-methyl-2-thiopseudourea. To 5.5 g. of cyanamide in 40 cc. of absolute ethanol was added (cooling in tap-water) 80 cc. of a solution of sodium ethoxide equivalent to 2.4 g. of sodium. Ten grams of isopropylisothiocyanate (8, 9)[6] was then added, again with slight cooling. After two hours at room temperature, the mixture was treated with 6 cc. of methyl iodide and allowed to stand overnight. The solution was concentrated to about 20 cc., diluted while hot with 40 cc. of water and chilled in ice. The yield of material melting at 113–116° was 12.3 g.; silky needles from water-ethanol, m.p. 117–118°.

Anal. Calc'd for $C_6H_{11}N_3S$: C, 45.84; H, 7.05.
Found: C, 45.65; H, 6.75.

*1-Isopropyl-5-(9-phenanthryl)biguanide hydrochloride.** The foregoing compound (2.5 g.) was desulfurized with 25 cc. of 15% alcoholic ammonia (7.5 hours at 100° under pressure). After evaporation of solvent, the resulting oily 1-cyano-3-isopropylguanidine, 2.7 g. of 9-phenanthrylamine hydrochloride, and 30 cc. of 95% ethanol were refluxed together for six hours. The alcohol was evaporated, after which the residue crystallized from acetone in a yield of 2.7 g., m.p. 225–230°. After two recrystallizations from absolute ethanol, the m.p. was 232–233°; oblong plates.

Anal. Calc'd for $C_{19}H_{22}ClN_5$: C, 64.12; H, 6.23.
Found: C, 63.97; H, 6.10.

The picrate crystallized from 95% ethanol in orange needles of m.p. 183.5–185°.

Anal. Calc'd for $C_{25}H_{24}N_8O_7$: C, 54.75; H, 4.41.
Found: C, 54.88; H, 4.29.

9-Phenanthrylisothiocyanate.[7] A suspension of 16.2 g. of 1,3-di-(9-phenanthryl)-thiourea (10) in 64 cc. of acetic anhydride was refluxed for one-half hour. On cooling overnight in the ice-box, 17.8 g. of a precipitate consisting of a mixture of 9-phenanthrylisothiocyanate (needles) and 9-acetylaminophenanthrene (prisms) separated. It was dissolved in 150 cc. of boiling acetic acid, the solution allowed to cool at room temperature, during 1.5–2 hours, and the resulting needles filtered quickly and washed with acetic acid; yield 6.7 g., m.p. 99.5–101.5°. The filtrate was concentrated to about 75 cc., 36 cc., of 24% HCl was added and the mixture heated just to boiling. The resulting supernatant liquid was decanted from some oil and the latter, recrystallized from acetic acid, yielded an additional 1.3 g. of the needles making the total yield 8.0 g. (82%). It crystallized from acetic acid or ethanol in long needles of m.p. 103–103.5°.

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[6] Isopropylthiourea, prepared from isopropylisothiocyanate and alcoholic ammonia melted at 167–167.5°. *Anal.* Calc'd for $C_4H_{10}N_2S$: N, 23.70. Found: N, 23.52. Jahn (8) reported the m.p. 157°. 1,3-Diisopropylthiourea, prepared from isopropylisothiocyanate gave the m.p. 139–141°. Jahn (8) reported the m.p. 161° for this compound, but Schmidt and Striewsky (9), who prepared it by another method, gave the m.p. 141–141.5°.

[7] A paper by Battegay and Boehler (11) on 1,3-dianthrylthioureas suggested this procedure. No experimental details were given.

Anal. Calc'd for $C_{15}H_9NS$: C, 76.56; H, 3.86.

Found: C, 76.28; H, 3.94.

The acetic acid-HCl solution above gave 8.0 g. of 9-phenanthrylamine hydrochloride after one hour of refluxing.

*1-Cyano-2-methyl-3-(9-phenanthryl)-2-thiopseudourea.** To 0.5 g. of sodium in 50 cc. of absolute ethanol was added 1.2 g. of cyanamide and 5.0 g. of 9-phenanthrylisothiocyanate and the mixture shaken for one to two hours. The clear solution was warmed slightly and 2.8 g. of methyl iodide was added. After one hour at room temperature followed by thorough cooling in ice, the yield of quite pure compound was 5.3 g. It crystallized from acetic acid or ethanol in broad needles of m.p. 188° with bubbling; a new solid formed and melted at 228–230.5°. If the temperature rise is slow the lower m.p. is not observed.

Anal. Calc'd for $C_{17}H_{13}N_3S$: C, 70.08; H, 4.50.

Found: C, 69.90; H, 4.64.

1-Cyano-3-(9-phenanthryl)guanidine (III). A mixture of 5.3 g. of the foregoing compound and 40 cc. of 10–15% alcoholic ammonia was heated in the steam-bath under pressure for five hours, and evaporated to dryness. The residue crystallized from 95% ethanol in a yield of 3.3 g. (70%), m.p. 182–186°. Two more recrystallizations gave the constant m.p. 189–190.5°; prisms.

Anal. Calc'd for $C_{16}H_{12}N_4$: C, 73.82; H, 4.65.

Found: C, 73.47; H, 4.64.

The compound is soluble in warm alkali, from which it can be precipitated, with acid, as a lower-melting (115–120°) form. Recrystallization gives again, the prisms of m.p. 189–190.5°.

*1,5-Di-(9-phenanthryl)biguanide hydrochloride**. 9-Phenanthrylamine hydrochloride (1.2 g.), 1.3 g. of III, and 15 cc. of 95% ethanol were refluxed together for seven hours. The fluffy solid (2.0 g., m.p. 237–244°) was recrystallized twice from aqueous ethanol-ether; fine needles, m.p. 245–247° (decomp.).

Anal. Calc'd for $C_{30}H_{24}ClN_5$: C, 73.53; H, 4.93; N, 14.29.

Found: C, 73.55; H, 4.70; N, 13.89.

*Conversion of III to the alkali-insoluble isomer of m.p. 212–213°**. A mixture of 0.5 g. of III, 0.2 g. of ethylamine hydrochloride, and 5 cc. of amyl alcohol was refluxed for seven hours. The solid hydrochloride (0.4 g., m.p. above 300°) which had separated during this time was converted to the base with warm dilute sodium hydroxide. The base crystallized from ethanol in long needles of m.p. 212–213°. Analysis showed it to be isomeric with III. It is alkali-insoluble.

Anal. Calc'd for $C_{16}H_{12}N_4$: C, 73.82; H, 4.65; N, 21.52; M.W., 260.

Found: C, 73.82; H, 4.78; N, 21.26; M.W., 269.

The same product was obtained in yields of 40–75% when ethylamine hydrochloride was replaced by diethyl- or dibutyl-amine hydrochloride.

SUMMARY

A series of guanidine and biguanide derivatives of phenanthrene have been synthesized and found to be ineffective against *gallinaceum* malaria in chicks.

BETHESDA 14, MARYLAND

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[Contribution from the Division of Physiology, National Institute of Health]

ATTEMPTS TO FIND NEW ANTIMALARIALS. XXII. BIGUANIDE DERIVATIVES OF PHENANTHRENE[1]

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In a foregoing communication (1), 1-isopropyl-5-(9-phenanthryl)biguanide (I), a phenanthrene analog of Paludrine (2), was reported to be ineffective against *gallinaceum* malaria in chicks. Since Paludrine contains chlorine, and as nuclear chlorine generally enhances antimalarial activity (3), a logical step appeared to be the synthesis of a representative of I containing this element.

$C_{14}H_9\text{-9-NHC(:NH)NHC(:NH)NH-}i\text{-}C_3H_7$ (I)

$C_{14}H_8\begin{cases}\text{3-Cl}\\ \text{6-NHC(:NH)NHC(:NH)NH-}i\text{-}C_3H_7\end{cases}$ (II)

$C_{14}H_9\text{-3-NHC(:NH)NHC(:NH)NH-}i\text{-}C_3H_7$ (III)

$C_{14}H_9\text{-9-NHC(:NH)NHCN (IV)} \xrightarrow{Me_2NH\cdot HCl} C_{14}H_9\text{-9-NHC(:NH)NHC(:NH)NMe}_2$ (V)

$C_{14}H_9\text{-9-N:C(SCH}_3\text{)NH}_2\text{ (VI)} \xrightarrow{NH_2C(:NH)NMe_2}$ No V

Accordingly, II was synthesized in a manner described previously (1) from 1-cyano-3-isopropylguanidine and 3-chloro-6-phenanthrylamine hydrochloride. The latter was obtained by a Beckmann rearrangement of the oxime of 3-chloro-6-acetylphenanthrene. For biological comparison, the chlorine-free analog (III) of II was likewise prepared from 3-phenanthrylamine hydrochloride.

Also included in this paper is 1,1-dimethyl-5-(9-phenanthryl)biguanide (V). Attempts to obtain V by the reaction of 2-methyl-1-(9-phenanthryl)-2-thiopseudourea (VI) with dimethylguanidine failed. Furthermore, previous efforts (1) to condense 1-cyano-3-(9-phenanthryl)guanidine (IV) with aliphatic amine hydrochlorides to give corresponding biguanides were unsuccessful. It has now been found that by fusing a mixture of IV and dimethylamine hydrochloride, V is formed in a yield of about 50%. Similarly, I could be prepared from IV and isopropylamine hydrochloride.

All of the compounds tested (II, III, and V) were inactive.

EXPERIMENTAL[2,3]

9-Phenanthrylthiourea. A mixture of 1.9 g. of 9-phenanthrylisothiocyanate (1), 20 cc. of ethanol, and 8 cc. of 10–15% alcoholic ammonia was shaken in a stoppered flask at 40° for 15–20 minutes. On cooling 1.9 g. of the thiourea was obtained, m.p. 201–203°. It crystallized from ethanol in thin rectangles of m.p. 203–204° (decomp.).

---

[1] The work described in this paper was done under a transfer of funds, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development to the National Institute of Health.

[2] All melting points are uncorrected.

[3] The microanalyses were carried out by C. A. Kinser and Betty Mount of this Laboratory.

Anal. Calc'd for $C_{15}H_{12}N_2S$: C, 71.42; H, 4.79.
Found: C, 71.37; H, 4.75.

2-Methyl-1-(9-phenanthryl)-2-thiopseudourea (VI). By refluxing together for ten minutes, 0.5 g. of 9-phenanthrylthiourea, 0.3 g. of methyl iodide, and 5 cc. of absolute ethanol, cooling, making slightly ammoniacal, and diluting with water, VI was obtained in a 0.5-g. yield. It crystallized from aqueous ethanol (Norit) in hexagons of m.p. 159–160°.

Anal. Calc'd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30.
Found: C, 72.11; H, 5.26.

Attempts to condense this compound with 1,1-dimethylguanidine to obtain the corresponding biguanide, were unsuccessful. It could, however, be desulfurized (15% alcoholic NH_3 at 100° in a sealed tube) to 9-phenanthrylguanidine, m.p. (hydrochloride) 256–258° (1).

3-Chloro-6-phenanthrylamine. A mixture of 4.2 g. of 3-chloro-6-acetylphenanthrene (3), 3.6 g. of hydroxylamine hydrochloride, 8 cc. of pyridine, and 25 cc. of absolute ethanol was refluxed for one-half hour and diluted with 5–10 cc. of water; yield of oxime 4.3 g., m.p. 211–213.5°. It was dissolved (warming) in 8 cc. of acetic anhydride and 16 cc. of acetic acid, and hydrogen chloride passed into the solution for three hours. Upon standing overnight, the yield of 3-chloro-6-acetylaminophenanthrene, m.p. 234–237°, was 4.2 g. A mixture of this, 32 cc. of acetic acid, and 32 cc. of 25% HCl was refluxed for 1.5 hours to give 3.5 g. of 3-chloro-6-phenanthrylamine hydrochloride (m.p. 260–264°, decomp.). The free base, prepared with dilute NH_4OH, melted at 156–157° after a recrystallization from ethanol followed by a high vacuum sublimation; thick plates.

Anal. Calc'd for $C_{14}H_{10}ClN$: C, 73.84; H, 4.43.
Found: C, 73.74; H, 4.39.

1-(3-Chloro-6-phenanthryl)-5-isopropylbiguanide hydrochloride (II). 1-Cyano-3-isopropyl-2-methyl-2-thiopseudourea (2.0 g.) was desulfurized with 20 cc. of 10–15% alcoholic NH_3 (7.5 hours in a sealed tube at 100°) to give 1.6 g. of oily 1-isopropyl-3-cyanoguanidine (1). A mixture of the latter, 2.4 g. of 3-chloro-6-phenanthrylamine hydrochloride, and 20 cc. of 95% ethanol was refluxed for 3.5 hours and diluted with 30 cc. of acetone. After thorough cooling in ice, 2.3 g. of II, m.p. 250–253° was obtained; fine, long needles from 95% ethanol, m.p. 251–252° (decomp.).

Anal. Calc'd for $C_{19}H_{21}Cl_2N_5$: C, 58.47; H, 5.42.
Found: C, 58.62; H, 5.45.

The picrate crystallized from 95% ethanol in orange prisms of m.p. 197–198° (sinters from 194°).

Anal. Calc'd for $C_{25}H_{23}ClN_8O_7$: C, 51.51; H, 3.98.
Found: C, 51.74; H, 4.21.

1-Isopropyl-5-(3-phenanthryl)biguanide hydrochloride (III). The 1-isopropyl-3-cyanoguanidine resulting from the desulfurization of 2.0 g. of the corresponding S-methyl compound (see previous experiment), 2.4 g. of 3-phenanthrylamine hydrochloride (4), and 18 cc. of 95% ethanol were refluxed together for 2.5 hours. The mixture was cooled in ice to give 2.1 g. of III of m.p. 256–259°; oblong plates from 95% ethanol, m.p. 257–258°.

Anal. Calc'd for $C_{19}H_{22}ClN_5$: C, 64.12; H, 6.23.
Found: C, 64.56; H, 6.45.

The picrate gave orange prisms from 95% ethanol, m.p. 214.5–216°.

Anal. Calc'd for $C_{25}H_{24}N_8O_7$: C, 54.75; H, 4.41.
Found: C, 54.94; H, 4.58.

1,1-Dimethyl-5-(9-phenanthryl)biguanide (V). An intimate mixture of 0.4 g. of IV (1) and 0.2 g. of dimethylamine hydrochloride was heated at 130–140° for one hour. Upon cooling, the melt solidified and was digested with boiling absolute ethanol. After filtering from insoluble material, diluting to turbidity with ether, and filtering again, 0.3 g. of prisms contaminated with a little dimethylamine hydrochloride separated. This was treated with dilute NH_4OH and the liberated base dried in ether and recrystallized from aqueous methanol; thin prisms of m.p. 133–135°.

Anal. Calc'd for $C_{18}H_{19}N_5$: C, 70.79; H, 6.27.
Found: C, 70.93; H, 6.03.

In a similar manner IV and isopropylamine hydrochloride gave the hydrochloride of I identical with that previously described (1).

SUMMARY

1-(3-Chloro-6-phenanthryl)-5-isopropylbiguanide, its chlorine-free analog and 1,1-dimethyl-5-(9-phenanthryl)biguanide have been synthesized as potential antimalarials. 3-Chloro-6-phenanthrylamine, an intermediate, was prepared by the Beckmann rearrangement of the oxime of 3-chloro-6-acetylphenanthrene.

BETHESDA 14, MD.

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[Contribution from the Chemotherapy Division, Stamford Research Laboratories, American Cyanamid Company]

HYDROLYSIS AND AMINOLYSIS OF CERTAIN METHOXYPYRIMIDINES

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Received January 6, 1947

In order to extend the study of the antimalarial activity (1) of certain phenylsulfonamidopyrimidines, members of this group containing the basic side chain associated with high activity in other series (2) were prepared. Although such a substitution had given rise (3) to an inactive sulfanilamide, 2-sulfanilamido-4-(3-diethylaminopropylamino)pyrimidine, the metanilamides were investigated since they have been shown (1) to act by a different mechanism. Furthermore, it was of interest to remove the amphoteric characteristics of such compounds by N-alkylation of the sulfonamide group.

To prepare these types of compounds it was planned to prepare the required 2-phenylsulfonamido-4-methoxypyrimidines, N-alkylate these, and replace the methoxyl with the desired side chain by a procedure which has been described (3). The second and third steps of this proposed scheme showed some interesting variations from their expected behavior. It is the purpose of this paper to describe the results with the *p*-chloro- and *m*-nitro-phenylsulfonamides.

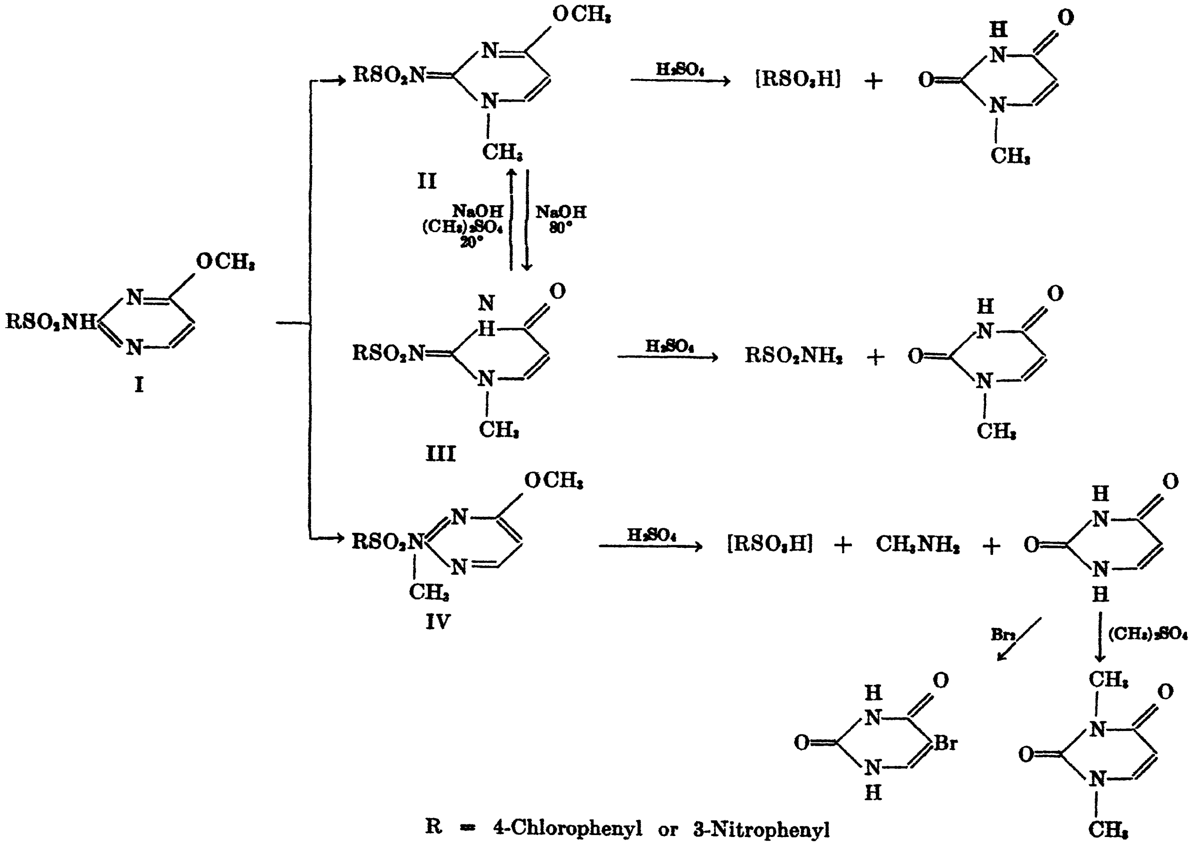
Methylation was effected either by diazomethane or by dimethyl sulfate and the results are summarized in Chart I. In the first method, alcohol rather than ether, which has been used previously (4), was employed as solvent to increase the speed of the reaction. Dimethyl sulfate was employed in aqueous alkali. With both reagents, the same two of the three possible monomethylated products were formed. This behavior is in contrast to that of 2-sulfanilamidopyrimidine reported here, and previous results with 2-metanilamidopyrimidine (1). These compounds give the N^1-methyl derivatives exclusively with diazomethane and 2-sulfanilamidopyrimidine is not alkylated satisfactorily with dimethyl sulfate (4).

The two products in both series were troublesome to separate, but solvent extraction was found to remove the lower-melting one preferentially in both cases. The structures of the methylated compounds were determined by degradation with 65% sulfuric acid at 140°. When the low-melting compounds (IV, Chart I) were treated with this reagent, uracil, confirmed by conversion into 5-bromouracil and 1,3-dimethyluracil, and a volatile organic base resulted. The high-melting isomers (II, Chart I) gave 1-methyluracil by this treatment. In this fashion it was established that the low-melting compounds (IV) were the N^1-methylated derivatives and the high-melting isomers (II) were the 1-methyl-2-phenylsulfonimido-1,2-dihydropyrimidines.

When dimethyl sulfate was used as the alkylating agent a third, alkali-soluble, product was formed. This compound was isomeric with the starting material and was shown to have structure III, or the tautomeric equivalents, by acid hydrolysis to 1-methyluracil. This material was found to originate from basic

CHART I

METHYLATION RESULTS WITH DIAZOMETHANE AND DIMETHYL SULFATE



R = 4-Chlorophenyl or 3-Nitrophenyl

hydrolysis of the alkylation product II rather than rearrangement[1] of I. In addition, the reverse change of III into II can be accomplished by alkylation with dimethyl sulfate at low temperature. This O-methylation is surprising, as uracil is reported to methylate only on the nitrogen (5).

The melting points of the two types of methylated products bear the same relation to each other as did the analogous products from sulfathiazole and sulfapyridine. There the N^1-methyl derivatives melted about 100° lower than the starting materials, and the ring N-methylated compounds had melting points approximating those of the starting materials (4).

The relative amounts of compounds of type IV to those of type II (Chart I) formed with the two reagents differed markedly. Diazomethane gave a ring-N to N^1-methyl ratio of 1:3 while with dimethyl sulfate the same ratio was 3.5:1. In the latter case the reaction was complicated by the hydrolysis of the methoxyl group which has been mentioned above. The rapid hydrolysis of the methoxy compounds (II) by dilute alkali at 80° was unexpected, since 2-sulfanilamido-4-methoxypyrimidine had been prepared by hydrolysis of the N^4-acetyl derivative with boiling 2.5 *N* alkali for one hour (6). In the present work, stability of the methoxyl groups to alkaline hydrolysis was found to be characteristic of the sulfonamides I, the N^1-methyl derivatives IV and of 2-amino-4-methoxypyrimidine. However, certain 2-amino alkoxypyrimidines do show instability (7) with respect to alkyl interchange but only on long heating with sodium alkoxides at 170°. The application of these or less drastic conditions to the types of compounds in Table I would be expected to reveal stability variations similar to those recorded.

In attempting the preparation of the proposed dialkylaminoalkylamino compounds it was found that 3-diethylaminopropylamine was considerably more reactive with the methoxypyrimidines (I) than was 5-diethylamino-2-pentylamine. A similar effect of the branching of chains on amine reactivity has been observed by Wright and Elderfield (8) in the case of α-bromo ketones.

The metanilamide, and the 3-nitro- and 4-chloro-phenylsulfonamides of structure I reacted at 110–120° with the substituted propylamine as did the analogous sulfanilamide (3). Although the ring N-methylated compounds of structure II were somewhat less reactive, the method was still applicable. 2-Amino-4-methoxypyrimidine required a much higher temperature, which is in keeping with the reported comparative reactivity of 2-sulfanilamido-4-methoxypyrimidine and 2-amino-4-methoxypyrimidine with ammonia (3). The N^1-methylated derivatives (structure IV) were essentially unreactive to 3-diethylaminopropylamine even at 190° where extensive decomposition occurred. A summary of the reactions which have been discussed above is shown in Table I.

It is readily seen that the reactions with aqueous alkali and with the amine are not parallel. The reactivity of the ring-N methylated compounds (II) might be explained on the basis of the similarity of their structure to an imino ether, which would be expected to behave in a similar manner. However, the "amidines" formed from II by amination (compounds L and N, Table II) are very stable to alkali. The difference between the unmethylated (I) and N^1-methylated (IV) compounds in their reaction with the amine is assumed to be due to the activating effect of the negative sulfonamide ion formed in the first case.

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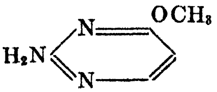
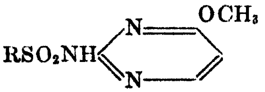
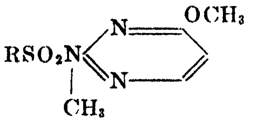
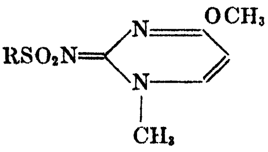
[1] Attempted rearrangement of the sulfonamides (I) with dimethyl sulfate in ethylene dichloride was unsuccessful; *cf.* Hilbert and Johnson, *J. Am. Chem. Soc.*, **52**, 2001 (1930).

The reduction of N^1-methyl-2-(*m*-nitrophenylsulfonamido)-4-methoxypyrimidine to the metanilamide proceeded smoothly with Raney nickel at 70° and 3 atmospheres. When the same conditions were used with 2-(3-nitrophenylsulfonimido)-1-methyl-4-(3-diethylaminopropylamino)-1,2-dihydropyrimidine, a complete conversion to the hydrazo compound took place.

TABLE I

Reactions of Methoxypyrimidine Derivatives

COMPOUND	EFFECT OF ALKALI	AMINATED BY $(C_2H_5)_2N(CH_2)_3NH_2$ at
	Unchanged	190°
	Unchanged	110–120°
	Unchanged	not at 190°
	Hydrolyzed	120–130°

The compounds listed in Table II showed no activity against a sporozoite-induced *Plasmodium gallinaceum* infection in chicks in tests conducted in this Laboratory under the direction of Dr. Sterling Brackett.

EXPERIMENTAL

4-Chlorobenzenesulfonyl Chloride (9)

From sodium 4-chlorobenzenesulfonate. Eighty-seven grams (0.405 mole) of finely powdered sodium 4-chlorobenzenesulfonate (Eastman White Label) was shaken with 84.6 g. (0.405 mole) of phosphorus pentachloride. Within five minutes the mixture liquefied and evolved heat. After standing for a half-hour, the slurry was heated on the steam-bath for another half-hour and then stirred into crushed ice and water. The resulting gummy

TABLE II

SULFONAMIDOPYRIMIDINE DERIVATIVES

	NAME	M.P.[a] °C.	EMPIRICAL FORMULA	ANALYSES,[b] %					
				Calc'd			Found		
				C	H	N	C	H	N
	4-Chlorophenylsulfonyl-								
A	-2-amino-4-methoxy-Pm[c]	244–245	$C_{11}H_{10}ClN_3O_3S$	44.1	3.4		44.2	3.4	
B	-2-imino-1-methyl-1,2-dihydro-pyrimidone-4	164–165	$C_{11}H_{10}ClN_3O_3S$	44.1	3.4	14.0	44.4	3.8	14.0
C	-2-methylamino-4-methoxy-Pm	85–86	$C_{12}H_{12}ClN_3O_3S$			13.4			13.3
D	-2-imino-1-methyl-4-methoxy-1,2-dihydro-Pm	211–212	$C_{12}H_{12}ClN_3O_3S$			13.4			13.1
	3-Nitrophenylsulfonyl-								
E	-2-imino-1-methyl-1,2-dihydro-pyrimidone-4[d]	207–208	$C_{11}H_{10}N_4O_5S$	42.6	3.3	18.1	42.7[e]	3.6	18.1
F	-2-methylamino-4-methoxy-Pm	115–116	$C_{12}H_{12}N_4O_5S$			17.3			17.2
G	-2-imino-1-methyl-4-methoxy-1,2-dihydro-Pm	216–217	$C_{12}H_{12}N_4O_5S$			17.3			17.1
H	N¹-methyl-2-metanilamido-4-methoxy-Pm	150–151	$C_{12}H_{14}N_4O_3S$			19.0			18.9
J	N¹-methyl-2-sulfanilamido-Pm	188–189	$C_{11}H_{12}N_4O_2S$	50.0	4.6	21.2	50.1	4.6	21.0
	4-Chlorophenylsulfonyl-								
K	-2-amino-4-(3-diethylaminopropylamino)-Pm	225–226	$C_{17}H_{24}ClN_5O_2S$	51.3	6.1	17.6	51.2[e]	6.3	17.4
L	-2-imino-1-methyl-4-(3-diethylaminopropylamino)-Pm	184–185	$C_{17}H_{26}ClN_5O_2S$	52.5	6.4	17.0	52.5[e]	6.6	17.1
M	2-Metanilamido-4-(3-diethylaminopropylamino)-Pm	225–227[f]	$C_{17}H_{26}N_6O_2S$	53.9	6.9	22.2	53.7	7.3	22.0
N	2-(3-Nitrophenylsulfonimido)-1-methyl-4-(3-diethylaminopropylamino)-1,2-dihydro-Pm	171	$C_{18}H_{26}N_6O_4S$	51.2		19.9	51.2[e]		20.0
O	1,2-bis[3-([1-Methyl-4-(3-diethylaminopropylamino)-2-pyrimidonyl]sulfamyl)phenyl]hydrazine	278–280[g]	$C_{36}H_{54}N_{12}O_4S_2$	55.2		21.5	55.3[e]		21.5

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[a] Corrected. The melting points above 200° were somewhat dependent on the rate of heating.

[b] Reported values are the average of two values differing by less than 0.3. Analyses were performed in this Laboratory under the direction of Dr. J. A. Kuck.

[c] Pm = Pyrimidine.

[d] Sulfur analysis—Calc'd 10.3%; found 10.5%.

[e] Determined by the Van Slyke wet combustion method.

[f] On rapid heating, melts sharply at 212°, resolidifies and melts completely at 225–227°. When heated slowly, sintering occurs at 212° and melting at 225–227°.

[g] With decomposition using rapid heating.

solid quickly turned to white platelets which were thoroughly washed with water and dried *in vacuo;* yield 95%; m.p. 51–53°. A trace of insoluble material and color was removed by recrystallization (charcoal) from petroleum ether (1–2 cc./g.); yield 85% of white needles melting at 52–54°.

From 4-chlorobenzenediazonium chloride. Meerwein *et al.* (10) reported an 80% yield of this sulfonyl chloride from "boiling under reflux a solution of 4-chlorobenzenediazonium chloride in liquid sulfur dioxide with anhydrous cupric chloride." Under the conditions described below, chlorine replacement was the main reaction with only a small amount of sulfonyl chloride formation.

A solution of 12.8 g. (0.1 mole) of 4-chloroaniline in 20 cc. of concentrated hydrochloric acid was treated with a 50% solution of 0.1 mole of sodium nitrite in the cold. This was then refluxed for one hour with several volumes of liquid sulfur dioxide and 14 g. of anhydrous cupric chloride. After allowing evaporation of most of the sulfur dioxide, crushed ice was added. A sample of the solid which separated gave some hydrochloric acid on heating with water. Conversion to 4-chlorobenzenesulfonamide (10) (m.p. 145°) with ammonia occurred to a small extent but the main product was a neutral substance melting at 53° [*p*-dichlorobenzene (11)] as does the desired sulfonyl chloride.

A similar experiment with 4-nitroaniline confirmed the predominance of chlorine replacement of the diazonium group by the formation of a neutral chloride. A small amount of 4-nitrobenzenesulfonyl chloride was demonstrated by conversion to the sulfonamide (12) (m.p. 178°) with ammonia.

When the diazotization of 4-chloroaniline was carried out with nitrosylsulfuric acid, the major portion of diazonium compound remained unchanged during the subsequent treatment.

2-(4-Chlorophenylsulfonamido)-4-methoxypyrimidine (A in Table II). A solution of 6.2 g. (0.05 mole) of 2-amino-4-methoxypyrimidine (13) and 13.3 g. (25% excess) of 4-chlorobenzenesulfonyl chloride in 8 cc. (0.1 mole) of dry pyridine was warmed to 60° and then cooled to keep the temperature below 70°. The reaction mixture which solidified within a half-hour was kept at 70–80° on the steam-bath for one hour. This crystalline solid was then separated from tne by-products by treatment with 20 cc. of boiling glacial acetic acid and filtration at 20°. The product was purified by recrystallization from glacial acetic acid (15 cc./g.) with charcoal treatment; yield 54%.

Because of the prevention of proper cooling by the solidification of the reaction mixture, on a larger scale the acid chloride must be added in two portions, allowing dissipation of the heat of reaction of each portion.

The same procedure was used to prepare *2-(3-nitrophenylsulfonamido)-4-methoxypyrimidine* (1) in 50% yield.

2-Metanilamido-4-methoxypyrimidine. A previous preparation (1) using a considerably longer heating time gave only about half the present yield due to the formation of an ammonia-insoluble by-product.

Thirty-two grams (0.103 mole) of 2-(3-nitrophenylsulfonamido)-4-methoxypyrimidin was dissolved in 130 cc. of commercial ammonium sulfide solution plus 60 cc. of concentrated ammonia. Vigorous boiling for seven minutes produced a yellow precipitate which was redissolved by addition of 130 cc. more sulfide solution. A second precipitation resulted after further boiling for eight minutes and the red-brown solution along with the precipitate was added to 100 cc. of 10 N acetic acid. The amine was purified by solution in ammonia (charcoal) and reprecipitation with dilute acetic acid; yield 89%.

Diazomethane Alkylation

Of 2-(3-nitrophenylsulfonamido)-4-methoxypyrimidine. The sulfonamide (62 g.) was powdered (80 mesh) and stirred in 600 cc. of absolute alcohol during the addition of 1–2 equivalents of diazomethane in ether. The reaction is conveniently conducted in a three-necked flask which is open to the air only through a long tube ending in a 1-mm. capillary tip. The reagent color was lost within twenty-five minutes and the mixture was then evaporated to dryness.

To remove the *N^1-methyl-N^1-(4-methoxy-2-pyrimidyl)-3-nitrobenzenesulfonamide* (Compound F, Table II), the powdered residue was shaken with 200 cc. of ethylene dichloride at not above 20–25° until the resulting semi-transparent "gel" had changed to a fine white powder. After filtration, this insoluble portion was separated by 125 cc. of 2.5 *N* sodium hydroxide into starting material (18% recovery) and a 20% yield of *2-(3-nitrophenylsulfonimido)-1-methyl-4-methoxy-1,2-dihydropyrimidine* (*G*). The latter was recrystallized from 95% alcohol (50 cc./g.), after another cold ethylene dichloride extraction if the melting point was broad.

The ethylene dichloride extract was evaporated to about 50 cc. and added to 4 volumes of methanol. This solution was seeded and set aside to crystallize slowly at 25°. When other conditions or other solvents were used, the product separated as an oil. The yield of *N^1-methyl-N^1-(4-methoxy-2-pyrimidyl)-3-nitrobenzenesulfonamide* obtained after work-up of the mother liquors amounted to about 60%.

Of 2-(4-chlorophenylsulfonamido)-4-methoxypyrimidine. In order to separate *N^1-methyl-N^1-(4-methoxy-2-pyrimidyl)-4-chlorobenzenesulfonamide* (*C*) from a similar alkylation mixture, it was necessary to use a warm U.S.P. ether (6 cc./g.) extraction of the powdered evaporation residue. This compound was recovered by evaporation and purified by solution in glacial acetic acid (2.5 cc./g.). After charcoal treatment, the material was crystallized by rapid addition of one volume of water to turbidity. From the ether-insoluble portion of the reaction mixture was obtained *2-(4-chlorophenylsulfonimido)-1-methyl-4-methoxy-1,2-dihydropyrimidine* (*D*) after removal of starting material with dilute alkali. This substance was recrystallized from hot glacial acetic acid (4 cc./g.). The yields of the two methyl derivatives were the same as obtained from the similar 3-nitro compound.

Of 2-sulfanilamidopyrimidine. Ether was used as a reaction medium rather than alcohol in order to minimize alkylation of the anilino nitrogen (4). By the procedure reported for the corresponding metanilamide (1), *N^1-methyl-2-sulfanilamidopyrimidine* (*J*) was prepared in 50% yield with a 40% recovery of starting material. Its structure was assumed by analogy to the metanilamide and this is supported by the relationship of its melting point to that of the starting material predicted on the basis of work on other phenylsulfonamidoheterocycles (1, 4).

Dimethylsulfate Alkylation

Of 2-(4-chlorophenylsulfonamido)-4-methoxypyrimidine. Thirty-six grams (0.12 mole) of sulfonamide was dissolved in 335 cc. (0.84 mole) of a 2.5 *N* mixture of potassium and ammonium hydroxides (in 5:1 molar ratio). Unlike sodium, potassium, or ammonium hydroxide, this mixture of alkalies keeps the starting material and the by-product (B) in solution. With smaller volumes per gram, as below, these two compounds can be separated by this mixed alkali. This was shaken with 57 cc. (0.6 mole) of dimethyl sulfate while cooling to maintain the temperature at 40–50°. The oil present changed to a granular solid at the conclusion of the reaction. This alkylation mixture was separated by the procedure given under diazomethane into a 20% yield of *N^1-methyl-N^1-(4-methoxy-2-pyrimidyl)-4-chlorobenzenesulfonamide* (*C*) and a 70% yield of *2-(4-chlorophenylsulfonimido)-1-methyl-4-methoxy-1,2-dihydropyrimidine* (*D*).

If the temperature is allowed to go to 70°, none of the latter compound is obtained and a corresponding increase in the yield of hydrolysis product (compound B, Table II) results. The reaction filtrate was precipitated by the addition of concentrated hydrochloric acid. The powdered precipitate was treated with vigorous shaking with the potassium-ammonium hydroxide mixture above (5 cc./g.) in which the starting material is extremely soluble. The solid dissolved and almost at once the salt of the isomeric *2-(4-chlorophenylsulfonimido)-1-methyl-1,2-dihydropyrimidone-4* (*B*) crystallized. This material was dissolved in warm water and added to dilute acetic acid. Final purification was accomplished by means of glacial acetic acid (2 cc./g.); yield 4%.

Of 2-(3-nitrophenylsulfonamido)-4-methoxypyrimidine. The same procedure as above was used except that sodium hydroxide was the most suitable alkali. The resulting alkylation mixture was separated by the method given under diazomethane into a 66% yield of *2-(3-nitrophenylsulfonimido)-1-methyl-4-methoxy-1,2-dihydropyrimidine* (*G*) and a 20% yield of *N^1-methyl-N^1-(4-methoxy-2-pyrimidyl)-3-nitrobenzenesulfonamide* (*F*).

The reaction filtrate was treated with one-third the original amount of dimethyl sulfate and enough 10 *N* sodium hydroxide to maintain alkalinity. After charcoal treatment, the solution was acidified and cooled. Another precipitation from alkali gave pure *2-(3-nitrophenylsulfonimido)-1-methyl-1,2-dihydropyrimidone-4* (*E*) in 10% yield. This material depressed the melting point of both the starting material and its high-melting methyl derivative (G).

Proof of Structure by Acid Degradation

Of low-melting compounds (*C and F, Table II*). One and a half grams of material was heated with 1.5 cc. of 68% sulfuric acid for one and a half hours in a bath at 145°. After addition of two volumes of cold water, the clear solution was neutralized to about *p*H 6 and evaporated to dryness *in vacuo*. A small portion of the residue, on careful extraction of the salt with cold water, gave an organic fraction melting above 300° (uracil melts at 330°).

The main portion of the powdered residue was used to prepare two derivatives. Half of this material was brominated in glacial acetic acid to give 5-bromouracil (14) melting at 293°. The other half of the residue was methylated with excess dimethyl sulfate and alkali to yield a compound melting at 123–124°. The melting point was not depressed by an authentic sample of 1,3-dimethyluracil (5b) prepared by the alkylation of uracil.

Of methyl derivatives (*B, D, E, and G*). The hydrolysis and evaporation to dryness were conducted as described above, except that 1 g. of material was used. In one case (B), the addition of water after hydrolysis caused the separation of white needles which were found to be 4-chlorobenzenesulfonamide (50% yield). After filtration, the neutralization and evaporation were carried out as before.

The powdered evaporation residue was washed with 5 cc. of cold absolute alcohol and then extracted twice with 13-cc. portions of hot alcohol. After evaporation of this extract to about 8 cc., a 70–80% yield of crude material (m.p. 215°) was obtained on cooling. Recrystallization from alcohol gave material melting at 235–236° and giving no depression of the melting point of authentic 1-methyluracil (15).

Interconversion of Methoxypyrimidines and Pyrimidones

Alkaline hydrolysis of methoxy compounds (*D and G*). The methoxypyrimidine (0.2 g.) was boiled for two minutes with 2 cc. of 50% alcohol and 1 cc. of 8 *N* potassium hydroxide, allowing evaporation of the alcohol. The resulting clear aqueous solution gave no evidence of starting material on dilution with ice. Precipitation with dilute hydrochloric acid gave products having the melting points of the pyrimidones B and E. These melting points were not depressed by mixing with samples of B and E isolated as by-products of the preparations of D and G employing dimethyl sulfate.

When the methoxy compounds A, C, and F and 2-amino-4-methoxypyrimidine were treated in the same way, no change in melting point nor appearance of alkali solubility (with the last three compounds) occurred. The 4-aminopyrimidines, L and N, which correspond to the unstable methoxy derivatives, D and G, gave the same evidences of stability.

Dimethyl sulfate alkylation of pyrimidones (*B and E*). The pyrimidone (0.3 g.) was dissolved in 9.2 cc. of water and 0.9 cc. of 8 *N* potassium hydroxide and shaken with 0.5 cc.

of dimethyl sulfate while maintaining the temperature at 20°. When the reaction was conducted at 50–60°, the starting material was recovered. After a half-hour the turbid mixture changed to a suspension of crystals. A neutral solid was obtained by filtering the alkaline liquid and washing well with water. Without further purification, the products melted at 212° (from B) and at 217° (from E) and showed no depression of the melting points of the corresponding methoxypyrimidines, D and G. Therefore, the sole course of the reaction seemed to be 0-methylation.

Unequivocal evidence for the O-methylation was obtained in two ways. The first was reconversion of the products to alkali-soluble materials which were shown to be the pyrimidones B and E by mixed melting point comparisons. The second method was amination with the liberation of methanol by 3-diethylaminopropylamine and formation of the acetic acid-soluble derivatives L and N. Neither of these reactions could occur with either of the two possible N-methyl products.

Amination of 4-methoxypyrimidines (A, D, and G) and 2-metanilamido-4-methoxypyrimidine with 3-diethylaminopropylamine. A mixture of one mole of methoxy compound A or the metanilamide and 1.5 moles of amine was immersed in a bath at 115° (130° for compounds D and G) and stirred to a thick syrup within a few minutes. A gas was evolved, and after about fifteen minutes the mixture was again stirred to control foaming during the solidification. The solid was heated for a total of one and a half hours and then ground to a paste with 600 cc. of water. The product was separated from a small amount of by-product by solution in 2.5 *N* acetic acid (2 cc./g.) and charcoal treatment. The material was recovered by precipitation with base (to *p*H 8) and seeding to prevent gumming. The base-soluble products (K and M in Table II) were then dissolved in 1 *N* alkali (4 cc./g.) and reprecipitated with dilute hydrochloric acid (to *p*H 8) with seeding. The N-methylated sulfonamides (L and N) were instead recrystallized from methanol (2 cc./g.). The yields were 70–80%.

An insoluble monohydrochloride (m.p. 274° dec.) of 2-(4-chlorophenylsulfonamido)-4-(3-diethylaminopropylamino)pyrimidine (K) was obtained by neutralization of an acid solution to *p*H 7–8. Acetic acid was used in the purifications for this reason and because it separated a small amount of by-product soluble in dilute hydrochloric acid.

When 2-amino-4-methoxypyrimidine was treated in the same manner at 115° for one-half hour or at 180° for ten minutes, 80% of the starting material was recovered. However, after one and a half hours at the latter temperature, no appreciable amount of starting material was present.

When the branched amine, 5-diethylamino-2-aminopentane, was heated with 2-(4-chlorophenylsulfonamido)-4-methoxypyrimidine (A) and 2-metanilamido-4-methoxypyrimidine for one and a half hours at 120°, the starting materials were recovered.

N^1-Methyl-2-metanilamido-4-methoxypyrimidine (H). Reduction of the corresponding nitro compound (F) with Raney nickel in absolute alcohol at three atmospheres pressure was complete in about half an hour at 70°. The product was recrystallized from methanol; yield 80%.

Hydrazo compound (O, Table II). Seventeen grams of the nitro intermediate (N) was dissolved in 100 cc. of absolute alcohol and shaken with Raney nickel under hydrogen at 40 lb. pressure. Absorption of 2.5 moles of hydrogen occurred rapidly and heavy crystallization took place. Addition of 1 mole of glacial acetic acid dissolved the solid and gave a neutral solution. Further treatment at this point with Raney nickel or platinum oxide did not carry the reduction on to the amine. After separation of the catalyst, the product was precipitated with alkali and recrystallized from methanol (20 cc./g.).

An alcoholic solution of the neutral acetate or a suspension of the white product in alkali became orange on aeration, presumably as a result of azo formation. The melting point and solubility of the product were not altered by stannous chloride treatment at 60° and only a small amount of diazotizable arylamine was formed.

SUMMARY

The alkylation of certain methoxypyrimidines with diazomethane and dimethyl sulfate has yielded a mixture of products whose quantitative relationship and structures have been determined.

A 4-pyrimidone derivative was found to alkylate exclusively on the oxygen with dimethyl sulfate.

The effect of structure on the stability of various methoxypyrimidines with respect to alkaline hydrolysis and to aminolysis has been investigated.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

SUBSTITUTED BROMOQUINOLINES[1]

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Very few bromoquinolines have been prepared from the corresponding 2- or 4-hydroxyquinoline by the reaction either with phosphorus pentabromide or phosphoryl tribromide. Claus and co-workers (1) have prepared 2-bromoquinoline and 4-bromoquinoline by the action phosphorus pentabromide on carbostyril and 4-hydroxyquinoline, respectively. Meyer and Heimann (2) prepared 2,4-dibromoquinoline in a similar manner from 4-hydroxycarbostyril. 4-Bromo-6-methoxyquinaldine has been prepared by Slater (3) through the action of phosphoryl tribromide on 4-hydroxy-6-methoxyquinaldine.

The present paper deals with the preparation of several bromoquinolines from the corresponding hydroxyquinolines, and the relative reactivity of the bromine and chlorine atom with some secondary amines. The replacement of the hydroxyl group by bromine proceeded smoothly, except in the case of 4-hydroxyquinaldine. In this instance about one-third of the product proved to be a dibromo compound. It would seem more reasonable that the extra bromine atom entered position 3 rather than anywhere in the benzene ring side. This bromination was probably due to the reaction between bromine, which resulted from the dissociation of phosphorus pentabromide, and 4-hydroxyquinaldine before replacement of the hydroxyl group. It would not seem likely that the second bromine atom entered the methyl group since no halogen test was obtained with alcoholic silver nitrate. Hammick (4) has reported that ω-bromoquinaldine does react readily with alcoholic silver nitrate solution. The behavior with sodium methoxide solution would indicate that one bromine atom (position 4) was much more reactive than the other one. Likewise, even though the one analysis leaves much to be desired, the condensation product of the dibromo compound and benzaldehyde certainly indicates that both bromine atoms remained in the molecule. Ozonization of the styryl derivative and decarboxylation of the acid gave a small amount of a compound which melted at 79–82°. The melting point of 3,4-dibromoquinoline has been reported as 82° (1b).

EXPERIMENTAL

Phosphoryl tribromide. The substance was prepared essentially according to the directions of Booth and Seegmiller (5). The method was modified slightly in that the phosphorus pentabromide was prepared in a finely divided form and the phosphoric anhydride-phosphorus pentabromide mixture was heated in an oil-bath at 100–103°. To reduce the formation of phosphorus tribromide by the decomposition of phosphorus pentabromide, excess bromine was added and then was removed in vacuum prior to vacuum distillation of the phosphoryl tribromide.

Phosphorus pentabromide. Finely divided phosphorus pentabromide was obtained by adding slowly the theoretical amount of phosphorus tribromide to a cold, vigorously stirred solution of 240 g. of bromine in 600–1000 ml. of low-boiling (30–60°) petroleum ether. The petroleum ether was decanted from the phosphorus pentabromide and the latter substance washed several times with petroleum ether and the last of the hydrocarbon removed in a vacuum desiccator. The yield was 628 g.

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[1] Constructed mainly from a Senior Thesis submitted by Max M. Marsh.

4-Hydroxyquinaldine. A solution of 46.5 g. (0.5 mole) of aniline and 63 g. (0.55 mole) of methyl acetoacetate in 150 ml. of methylene chloride and 2 drops of dilute hydrochloric acid was refluxed, using a water trap with the reflux condenser, until no more water was collected. Most of the methylene chloride was removed by distillation, then the last of the solvent removed in vacuum, and enough warm phenyl ether added to the crude methyl β-anilinocrotonate to dissolve it. The phenyl ether solution of the crude anilinocrotonate was added to 350 ml. of boiling phenyl ether at a rate which did not allow the temperature to fall below 245°. The heating was continued until no more methyl alcohol distilled from the reaction mixture. After the solution cooled to room temperature, 75–100 ml. of low-boiling ligroin was added, the 4-hydroxyquinaldine removed and washed with three 100-ml. portions of petroleum ether, and dried at 80°. The yield was 71.4 g. (89.8%); m.p. 226–228.5°.

The substance was pure enough for subsequent work but may be recrystallized from ethyl alcohol; m.p. 229–230° [Lit. (7), 230–231°].

2-Bromolepidine. 4-Methylcarbostyril (118 g.; 0.75 mole) was mixed with 215 g. (0.75 mole) of phosphoryl tribromide and heated in an oil-bath at 120°. The mixture liquefied in about thirty minutes, then solidified completely, but it was heated for another hour. The reaction mixture was treated cautiously with ice, and after about 50 g. of ice had been added, it was poured into 800 ml. of ice and water. The 2-bromolepidine was precipitated by addition of sodium hydroxide solution while the temperature was kept down by the addition of ice. The solid was washed successively with water, one per cent sodium bicarbonate solution, then water, and finally dried in air at 50°. The yield of crude 2-bromolepidine was 151 g. (90.7%); m.p. 73–75°. A 25-g. portion was recrystallized from ethyl alcohol and from ligroin (b.p. 55–65°) giving 17.5 g. which melted at 81–81.5°; b.p. 125–126° (1 mm.).

Anal. Calc'd for $C_{10}H_8BrN$: N, 6.30. Found: N, 6.11.

Similar results were obtained using phosphorus pentabromide.

2-Bromo-6-methoxylepidine. Five and five-tenths grams (0.029 mole) of 2-hydroxy-6-methoxylepidine and 18 g. (0.027 mole) of phosphorus pentabromide were mixed thoroughly then heated at 70–80° for thirty minutes and at 120° for one hour. After hydrolysis of the reaction mixture with ice and water, and neutralization of the solution with sodium hydroxide, the solid was washed, and recrystallized from 20 ml. of a benzene-ligroin mixture (1:1). The yield of 2-bromo-6-methoxylepidine was 2.8 g. (42%); m.p. 137–142°. Recrystallization of one gram of the substance from 20 ml. of ethyl alcohol gave short, white needles of 2-bromo-6-methoxylepidine melting at 144–145°.

Anal. Calc'd for $C_{11}H_{10}BrNO$: Br, 31.70. Found: Br, 31.77.

4-Bromoquinaldine. This substance was prepared like the 2-bromo-6-methoxylepidine, using 20 g. (0.126 mole) of 4-hydroxyquinaldine and 30 g. (0.07 mole) of phosphorus pentabromide. The crude bromo compound was extracted with 50 ml. portions of hot ligroin (b.p. 60–90°), the ligroin extracts concentrated to 35–40 ml., and refrigerated. Five grams of a white crystalline solid, A, which melted at 84.5–85.5° was obtained. (This substance was subsequently shown to be 3,4-dibromoquinaldine.) After removal of the ligroin from the filtrate, it was distilled in vacuum to give 7 g. (25.2%) of 4-bromoquinaldine; b.p. 88–90° (1 mm.).

Anal. Calc'd for $C_{10}H_8BrN$: Br. 35.99. Found: Br, 35.61.

3,4-Dibromoquinaldine (A). The substance gave no precipitate with alcoholic silver nitrate.

Anal. Calc'd for $C_{10}H_7Br_2N$: Br. 53.11. Found: Br, 53.05.

3-Bromo-4-methoxyquinaldine. Four grams (0.013 mole) of substance A was refluxed for five hours with a solution of 1 g. of sodium in 20 ml. of methanol, then the solution diluted with 150 ml. of water and allowed to stand in an ice-bath. The solid was first recrystallized from ethyl alcohol, then from ligroin (b.p. 60–90°). The yield of white crystalline solid was 2.2 g. (68.8%); m.p. 54–56°.

Anal. Calc'd for $C_{11}H_{10}BrNO$: Br, 31.70. Found: Br, 31.76.

3,4-Dibromo-2-styrylquinoline. Three grams (0.01 mole) of substance A was heated with 1.1 g. of freshly distilled benzaldehyde and 2 g. of anhydrous zinc chloride for 2.5 hours. After cooling, it was extracted twice with concentrated hydrochloric acid, then washed with dilute sodium bicarbonate solution, dried, and recrystallized from benzene. A yield of 0.4 g. of a yellow microcrystalline solid was obtained; m.p. 145.5–147°.

Anal. Calc'd for $C_{17}H_{11}Br_2N$: Br, 41.08. Found: Br, 42.56.

Two-tenths gram of the above styryl derivative was suspended in 20 ml. of glacial acetic acid and ozonized to the corresponding carboxylic acid according to the method of Kaslow and Stayner (6). One-tenth gram of an acid which melted with decomposition at 132–133° was obtained; presumably this substance is 3,4-dibromoquinaldic acid. The acid was decarboxylated by heating in an oil-bath at 150°. The fused mass was dissolved in 5 ml. of hot ethyl alcohol, and water was added dropwise until a faint cloudiness was produced. A yield of 15 mg. of a microcrystalline solid was obtained; m.p. 79–82°. This value checks the melting point recorded for 3,4-dibromoquinoline (1b).

Ethyl 4-bromoquinaldate. This substance was prepared in an entirely analogous manner from 8 g. (0.037 mole) of ethyl 4-hydroxyquinaldate and 10 g. (0.023 mole) of phosphorus pentabromide as described for 4-bromo-6-methoxyquinaldine. After purification by recrystallization from a benzene-ligroin solution (10:1), a yield of 6 g. (58.3%) of light tan crystals was obtained; m.p. 91–92°. An additional 2 g. of lower-melting material was obtained from the mother liquor.

Anal. Calc'd for $C_{12}H_{10}BrNO_2$: Br, 28.53. Found: Br, 28.54.

4-Bromoquinaldic acid. Five grams (0.018 mole) of ethyl 4-bromoquinaldate was refluxed for 24 hours with a solution of 1.5 g. (0.038 mole) of sodium hydroxide in 30 ml. of water. The cooled solution was acidified with just enough dilute hydrochloric acid to dissolve the solid, then dilute ammonia water was added until no more precipitation occurred. The solid was recrystallized from 80% ethyl alcohol. A yield of 3.5 g. (77.8%) of fine, light tan needles was obtained; m.p. 159–164° (dec.). Further recrystallization did not change the decomposition temperature.

Anal. Calc'd for $C_{10}H_6BrNO_2$: Br, 31.71. Found: Br, 31.97.

6-Methoxy-2-piperidinolepidine. A solution of 2.42 g. (0.01 mole) of 2-bromo-6-methoxylepidine in 5 ml. of piperidine was refluxed for four hours, the solution diluted with 100 ml. of water, and the solid removed and recrystallized from ethyl alcohol; a yield of 1.9 g (77%) of light colored solid was obtained; m.p. 96.5-98°. [Lit. (8), m.p. 97° yield 61%].

2-Morpholinolepidine monohydrochloride. A solution of 2.5 g. (0.0112 mole) of 2-bromolepidine in 5 ml. of morpholine was heated on the steam-bath for five hours, then cooled, diluted with 100 ml. of water, the oil extracted, dried, and the solvent removed by distillation. The residue was dissolved in 25 ml. of absolute ethyl alcohol and dry hydrogen chloride bubbled into the solution until no more precipitate formed. The yield of monohydrochloride was 3 g. (99%); it melted with decomposition at 250–255°. The substance may be recrystallized from absolute ethyl alcohol.

Anal. Calc'd for $C_{14}H_{17}ClNO_2$: Cl, 13.39. Found: Cl, 13.24.

Under identical conditions of reaction and isolation, 2 g. (0.0112 mole) of 2-chlorolepidine gave 2.35 g. (78%) yield of 2-morpholinolepidine monohydrochloride.

SUMMARY

The preparation of 2-bromolepidine, 2-bromo-6-methoxylepidine, 4-bromoquinaldine, ethyl 4-bromoquinaldate, and 4-bromoquinaldic acid has been described. A by-product formed during the preparation of 4-bromoquinaldine has been tentatively identified as 3,4-dibromoquinaldine. It has been shown

that 2-bromolepidine and 2-bromo-6-methoxylepidine react faster with morpholine and piperidine, respectively, than do the corresponding 2-chloro compounds.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

α-OXIMINO ACID INTERMEDIATES FOR THE SYNTHESIS OF α-AMINO ACIDS[1]

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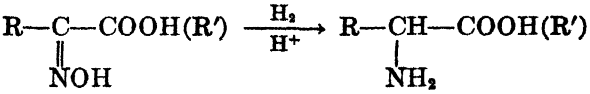
The catalytic hydrogenation of α-oximino acids or esters affords a convenient method for the synthesis of α-amino acids (1):



$$\mathrm{R{-}\underset{\underset{NOH}{\|}}{C}{-}COOH(R')} \xrightarrow[\mathrm{H^+}]{\mathrm{H_2}} \mathrm{R{-}\underset{\underset{NH_2}{|}}{CH}{-}COOH(R')}$$

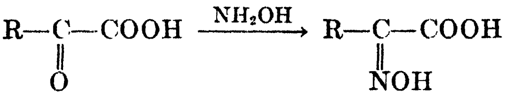
If the appropriate α-oximino intermediates are made available, it should be possible to synthesize many of the naturally occurring amino acids as well as their homologs, analogs, and derivatives.

It is of interest to note that α-oximino intermediates may be converted into amino acids by biological processes. Virtanen (2) found oximinosuccinic acid among the extraction products of root nodules of leguminous plants and postulated it as the precursor of *l*-aspartic acid. Maurer (3) has shown that actively fermenting yeast reduces α-oximinopropionic acid to alanine.

A brief survey, with more complete bibliography, of the methods by which α-oximino acids or esters have been prepared appears timely.

α-Oximino acids or esters may be prepared from (a) α-keto acids or esters; (b) α-halogen acids or esters; (c) substituted acetoacetic or malonic esters; and (d) substituted malonic acids.

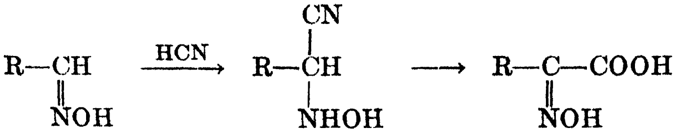
a. Preparation from α-keto acids or esters. α-Oximino acids were first prepared from the corresponding α-keto acid and hydroxylamine (4):



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}COOH} \xrightarrow{\mathrm{NH_2OH}} \mathrm{R{-}\underset{\underset{NOH}{\|}}{C}{-}COOH}$$

Thus alanine was obtained by the reduction of the oxime of pyruvic acid (5), aspartic acid from oxalacetic acid (6), glutamic acid from α-ketoglutaric acid (7), and phenylalanine from phenylpyruvic acid (8) and its thioketo analog (9). Unfortunately, the number of α-keto acids is very limited.

The procedure of Miller and Plöchl (10), which may be summarized by the equation:



$$\mathrm{R{-}\underset{\underset{NOH}{\|}}{CH}} \xrightarrow{\mathrm{HCN}} \mathrm{R{-}\overset{\overset{CN}{|}}{\underset{\underset{NHOH}{|}}{CH}}} \longrightarrow \mathrm{R{-}\underset{\underset{NOH}{\|}}{C}{-}COOH}$$

has not been developed to a practical stage.

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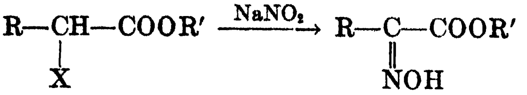
[1] Sixth paper on the synthesis of amino acids. For the fifth paper, see Mattocks and Hartung, *J. Am. Chem. Soc.*, **68**, 2108 (1946).

[2] Present address: The Maltbie Chemical Co., Newark, N. J.

b. Preparation from α-halogen esters. α-Oximino esters may be prepared from α-halogen esters, using sodium nitrite in aqueous ethanol and allowing to stand for 3–4 weeks.



$$R\text{—}\underset{\underset{\displaystyle X}{|}}{CH}\text{—}COOR' \xrightarrow{NaNO_2} R\text{—}\underset{\underset{\displaystyle NOH}{\|}}{C}\text{—}COOR'$$

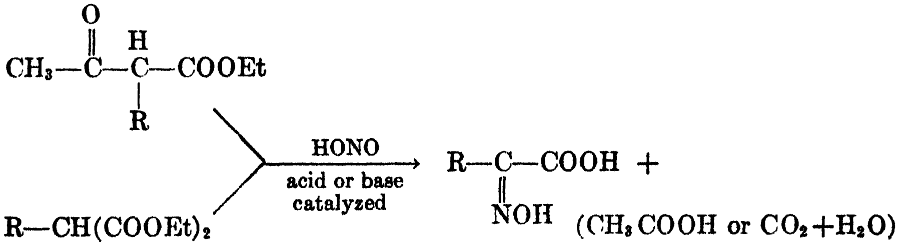
Yields up to 65% have been reported (11) and similar results were obtained in these Laboratories (1). Hydroxylamine may be employed in place of nitrite in a similar manner (12). These methods have not been widely used for the synthesis of α-oximino compounds.

c. Preparation from acetoacetic and malonic esters. The nitrosation of acetoacetic and malonic ester derivatives, with or without solvent, has been carried out with oxides of nitrogen, inorganic and organic nitrites under acidic or basic conditions.

Unsubstituted β-keto esters react with nitrites to form β-keto-α-oximino esters, $R\text{—}\underset{\underset{\displaystyle O}{\|}}{C}\text{—}C(:NOH)\text{—}COOR'$ (13, 14). Isonitrosoacetoacetic ester, $CH_3C\text{—}C(:NOH)\text{—}COOR'$, has been used in the synthesis of threonine (15). Ethyl α-isonitrosoacetonedicarboxylate (16) has been used for the synthesis of β-hydroxyglutamic acid (21, 22).

Diethyl malonate forms excellent yields (23–27) of diethyl oximinomalonate; on reduction the aminomalonic ester is formed, which, after acetylation or benzoylation serves as an excellent intermediate for the synthesis of tryptophane and other amino acids (24, 28–30).

The *monosubstituted* acetoacetic and malonic esters react with nitrites under proper conditions (31) losing an acyl or carbalkoxyl group,[3] e.g.:



$$\left.\begin{array}{l} CH_3\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}\underset{\underset{\displaystyle R}{|}}{\overset{H}{C}}\text{—}COOEt \\ R\text{—}CH(COOEt)_2 \end{array}\right\rangle \xrightarrow[\text{acid or base catalyzed}]{HONO} R\text{—}\underset{\underset{\displaystyle NOH}{\|}}{C}\text{—}COOH + (CH_3COOH \text{ or } CO_2 + H_2O)$$

In a similar manner α-carbethoxybutyrolactone and α-acetylbutyrolactone (32)

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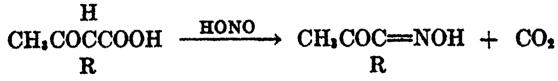
[3] If the β-keto *acid* is nitrosated, the carboxyl group is removed and the product is an α-oximinoalkyl methyl ketone, *e.g.*:

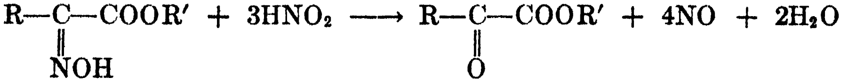


$$CH_3CO\underset{R}{\overset{H}{C}}COOH \xrightarrow{HONO} CH_3CO\underset{R}{C}{=}NOH + CO_2$$

This type of reaction was employed (17–19) for the preparation of diisonitrosoacetone from acetonedicarboxylic acid in the synthesis of histidine (20).

react with nitrous acid to give α-oximinobutyrolactone. The latter has been used in the synthesis of methionine (33).

The ease of replacement of the acyl group has been reported to decrease in the order —CHO, —$COCH_3$, —COC_6H_5 (31). Excess nitrite is reported (34) to cause removal of the α-oximino group and formation of the α-keto acid, according to the equation:



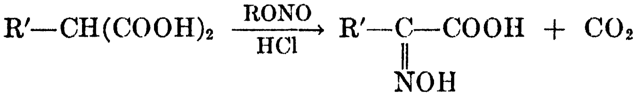
$$\mathrm{R{-}\underset{\underset{NOH}{\|}}{C}{-}COOR' + 3HNO_2 \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}COOR' + 4NO + 2H_2O}$$

The acid or alkali catalyzed nitrosation of substituted acetoacetic and malonic esters by oxides of nitrogen (31, 35–38) or alkali nitrites (39–43) in aqueous or alcoholic media was used by earlier workers. These methods are not generally satisfactory and have been displaced by more convenient procedures.

When the nitrosation of substituted acetoacetic and malonic esters is carried out with alkyl nitrite and alkoxides in ethanol or ether, good yields of α-oximino compounds are obtained.[4] This method has been employed to prepare many α-amino acid precursors (44–48), and is useful where an acid-catalyzed nitrosation is undesirable.

A very useful acid-catalyzed nitrosation of α-substituted acetoacetic esters employs nitrosyl sulfate in sulfuric acid (1, 49–55). Excellent yields (80–90%) of many α-oximino acids and esters have been reported and a modification of this procedure in these Laboratories has been described (1), and will be discussed later.

d. Preparation from substituted malonic acids. When substituted malonic acids in ether are allowed to react with alkyl nitrite and hydrogen chloride (56), α-oximino acids are produced:



$$\mathrm{R'{-}CH(COOH)_2 \xrightarrow[HCl]{RONO} R'{-}\underset{\underset{NOH}{\|}}{C}{-}COOH + CO_2}$$

This method, modifications of which are described in the experimental part, gives excellent yields (85–92%) of desired intermediates for α-amino acids.

Mechanism of the nitrosation of β-keto esters and malonic ester derivatives. The following rule has been stated (51) with regard to the nitrosation of β-keto esters: "When nitrous acid or its derivatives act on an α-substituted β-keto ester, the latter reacting in its enol form gives an α-oximino acid or ester." According to this rule the probable mechanism of the nitrosation may be illustrated by the equations:[5]

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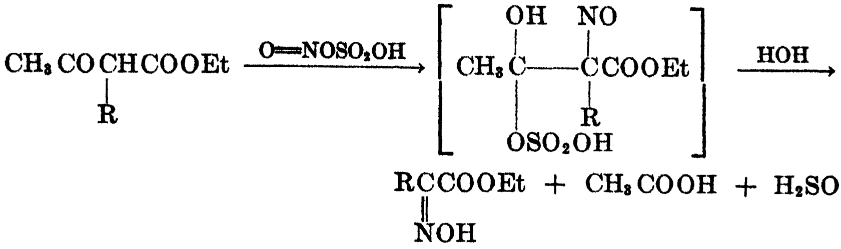
[4] A manuscript in preparation by Shivers and Hauser, sent to us through the courtesy of Dr. C. R. Hauser, describes their excellent results in preparing α-oximino esters from alkylmalonic esters.

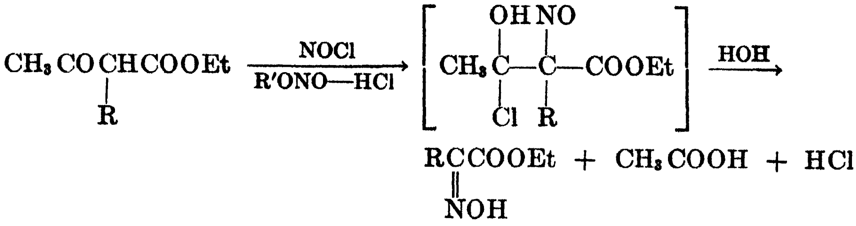
[5] In equations II and IV, nitrosyl chloride (NOCl) is presumed to be formed from R′ONO and HCl.

I.



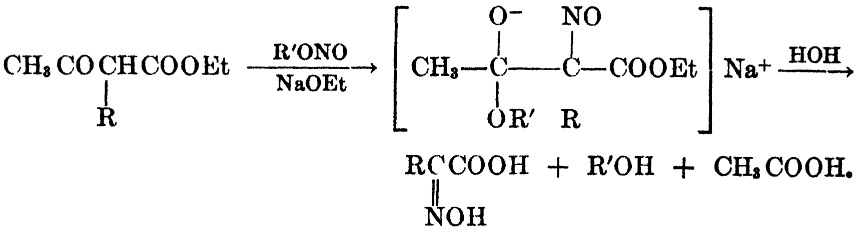
$$\mathrm{CH_3CO\underset{\underset{R}{|}}{C}HCOOEt} \xrightarrow{\mathrm{O{=}NOSO_2OH}} \left[\mathrm{CH_3\overset{\overset{OH}{|}}{\underset{\underset{OSO_2OH}{|}}{C}}\text{——}\overset{\overset{NO}{|}}{\underset{\underset{R}{|}}{C}}COOEt}\right] \xrightarrow{\mathrm{HOH}} \mathrm{R\underset{\underset{NOH}{\|}}{C}COOEt + CH_3COOH + H_2SO_4}$$

II.



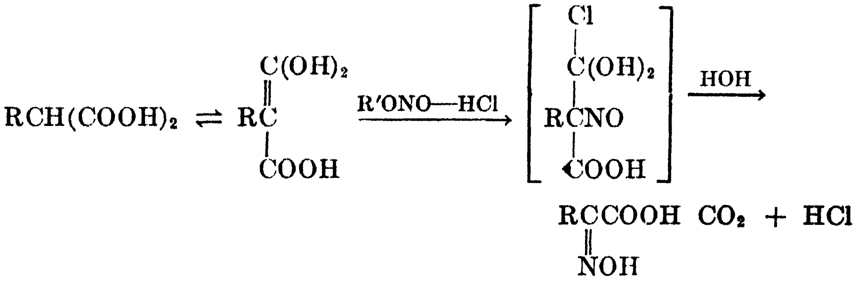
$$\mathrm{CH_3CO\underset{\underset{R}{|}}{C}HCOOEt} \xrightarrow[\mathrm{R'ONO\text{—}HCl}]{\mathrm{NOCl}} \left[\mathrm{CH_3\overset{\overset{OH}{|}}{\underset{\underset{Cl}{|}}{C}}\text{—}\overset{\overset{NO}{|}}{\underset{\underset{R}{|}}{C}}\text{—}COOEt}\right] \xrightarrow{\mathrm{HOH}} \mathrm{R\underset{\underset{NOH}{\|}}{C}COOEt + CH_3COOH + HCl}$$

III.



$$\mathrm{CH_3CO\underset{\underset{R}{|}}{C}HCOOEt} \xrightarrow[\mathrm{NaOEt}]{\mathrm{R'ONO}} \left[\mathrm{CH_3\text{—}\overset{\overset{O^-}{|}}{\underset{\underset{OR'}{|}}{C}}\text{——}\overset{\overset{NO}{|}}{\underset{\underset{R}{|}}{C}}\text{—}COOEt}\right]\mathrm{Na^+} \xrightarrow{\mathrm{HOH}} \mathrm{R\underset{\underset{NOH}{\|}}{C}COOH + R'OH + CH_3COOH.}$$

IV.



$$\mathrm{RCH(COOH)_2} \rightleftharpoons \mathrm{R\overset{\overset{C(OH)_2}{\|}}{\underset{\underset{COOH}{|}}{C}}} \xrightarrow{\mathrm{R'ONO\text{—}HCl}} \left[\mathrm{R\overset{\overset{\overset{Cl}{|}}{C(OH)_2}}{\underset{\underset{COOH}{|}}{\overset{|}{C}}}NO}\right] \xrightarrow{\mathrm{HOH}} \mathrm{R\underset{\underset{NOH}{\|}}{C}COOH\ \ CO_2 + HCl}$$

Our observations on the syntheses of α-oximino acids from α-halogen acids by an adaptation of the nitrosyl sulfate reaction on ethyl alkylacetoacetates have been described (1). It was found that an alkyl nitrite reacting with the ester in 85% sulfuric acid, gives good yields of pure alkoximino acid. Further application of this method now reveals that the conditions are too drastic for some intermediates, particularly those containing a substituent sensitive to high concentration of sulfuric acid. Hence a further study of the various nitrosation reactions was made to overcome objectionable features in the methods and to find more suitable conditions for the preparation of certain α-amino acid intermediates.

Three methods were examined in some detail: (a) a further study of the reaction with alkyl nitrite and ethyl alkylacetoacetate in sulfuric acid; (b) the reaction of ethyl alkylacetoacetate and diethyl alkylmalonates with alkyl nitrite in ethanolic sodium ethoxide; (c) the reaction of alkylmalonic acids, in ether solution, with alkyl nitrite in the presence of hydrogen chloride. The latter method has been found most satisfactory for the preparation of α-oximino acids, where it is possible to obtain the desired monosubstituted malonic acid.

EXPERIMENTAL

Preparation of intermediates. The substituted acetoacetic and malonic esters were prepared by the usual alkylation procedure, using 1.5 equivalents of ester and one equivalent each of sodium and alkyl halide in absolute ethanol. The malonic acids were prepared by saponification of the substituted malonic esters.

Butyl nitrite was prepared by a modification[6] of the method of Noyes (57). The rate of addition of acid to the sodium nitrite-butyl alcohol mixture may be increased considerably, and the time required to complete the addition of acid reduced from two hours to twenty or thirty minutes if the water used in the Noyes procedure is replaced by an equal weight of crushed ice. From 457 ml. of *n*-butyl alcohol was obtained 417 g. of *n*-butyl nitrite (81%). Isopropyl nitrite may also be prepared in this manner and gives comparable results in nitrosation procedures.

Melting points reported are uncorrected.

Nitrosation of ethyl alkylacetoacetates in acid (Method A). As typical for this procedure, the synthesis of α-oximinocaproic acid is described. In a 400-ml. beaker surrounded by an ice-salt bath was placed 30 g. of 85% sulfuric acid. Mechanical stirring was provided (a 4-blade "paddle" stirrer was found most efficient) and when the temperature of the acid reached −5–0°, 18.6 g. (0.1 mole) ethyl *n*-butylacetoacetate was added slowly, avoiding a rise in temperature. When all was added, 11 g. (0.1 mole plus 5% excess) of butyl nitrite was slowly added dropwise, keeping the temperature as near as 0° as possible. Slow effervescence was observed, but if the nitrite was added too rapidly, oxides of nitrogen were evolved. After all the nitrite was added, small pieces of ice were added to dilute the acid. At this point a white curdy precipitate of oximino ester appeared. Cold water was then added and the liquid extracted with ether. The oximino compound was extracted from the ether by cold 10% NaOH. The red alkaline extract was heated on the steam-bath for 15 minutes, then cooled and acidified. The precipitated α-oximinocaproic acid was filtered off and the filtrate extracted with ether. The product was recrystallized from benzin and melted at 136° (dec.) yield 86%. Schmidt and Dieterle (31) reported 132° (dec.).

α-Oximino-β-phenylpropionic acid, m.p. 165° (dec.) was obtained from ethyl benzylacetoacetate, using the procedure described, in yields of 85%. The reported melting points for this compound are 167° (58), 168° (1). When two-thirds of the sulfuric acid was replaced by phosphoric acid (85%), the yield of crude α-oximino-β-phenylpropionic acid was 45%. When acetic anhydride or formic acid (85%) replaced the sulfuric acid, the yield of product was still lower. When dry hydrogen chloride was passed through an ethereal solution of ethyl benzylacetoacetate and butyl nitrite, the reaction mixture turned deep red and the yield of crude oximino acid was 52%. When recrystallized from dilute ethanol, the acid melted at 165°.

When ethyl 3,4-diethoxybenzylacetoacetate was treated in 85% sulfuric acid with alkyl nitrite, the reaction mixture darkened and none of the desired oximino derivative could be isolated.

Nitrosation of ethyl alkylacetoacetates and diethyl alklymalonates under alkaline conditions (Method B). The synthesis of α-oximino-β-phenylpropionic acid is typical for this procedure. In a 250-ml. 3-neck flask fitted with mechanical stirrer, dropping-funnel, and reflux condenser was placed 50 ml. of absolute ethanol in which was dissolved 2.3 g. of sodium. To the cooled and stirred solution was added 25 g. (0.1 mole) of benzylmalonic ester. The flask was surrounded by a cold (10°) water-bath, and 11.6 g. (0.1 mole plus 10% excess) of butyl nitrite was added slowly through the dropping-funnel over a period of 15 minutes, with rapid stirring. Stirring was continued for 30 minutes after addition of the nitrite; then the ethanol and butanol were removed on the water-bath under reduced pressure. Thirty grams of crushed ice was added to the residue. The solution was acidified with 6 *N* sulfuric acid and extracted with ether. The ethereal layer was thoroughly extracted with 10% NaOH solution. To obtain the free oximino acid, the alkaline extract was warmed on the steam-bath for 15 minutes to ensure saponification of the oximino ester. The solution was then chilled and carefully acidified with conc'd HCl. The α-oximino-β-phenylpropionic acid was recrystallized from dilute alcohol. The yield of product melting at 165° (dec.) was 13–14 g. (75%). A 62% yield of this compound was obtained from the nitrosation of benzylacetoacetic ester by this procedure.

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[6] The authors are indebted to Dr. K. E. Hamlin, Jr. for this modification.

One-tenth mole (18.8 g.) of diethyl ethylmalonate nitrosated according to Method B gave a 65% yield of α-oximinobutyric acid. In the case of the lower molecular weight α-oximino acids, which are more soluble in water, extraction with ether after the final acidification was necessary. After removal of the ether, the oximino acids were recrystallized from water or dilute ethanol. The α-oximinobutyric acid was recrystallized from ether-benzin and melted at 154° (dec.). The reported value is 154–155° (54, 1).

In a similar manner, a 70% yield of α-oximino-*n*-caproic acid was obtained from 0.1 mole (21.6 g.) of *n*-butylmalonic ester. The product, recrystallized from ether-benzin, melted at 135° (dec.). Hamlin and Hartung (1) reported 137°.

Nitrosation of alkylmalonic acids (Method C). As typical of this modification, the synthesis of α-oximino-β-phenylpropionic acid is described. In a small beaker surrounded by an ice-salt bath, 4 g. (0.02 mole) of benzylmalonic acid was dissolved in 25 ml. of ether. To it was added with stirring 4.5 g. (0.04 mole) of *n*-butyl nitrite and dry HCl was slowly passed into the solution. The reaction mixture became reddish brown and the odor of nitrosyl chloride was present. After 25 minutes, a solid appeared which increased as some of the ether evaporated. At this point, the remainder of the ether was evaporated, cold water was added, and the precipitate filtered off. The nearly-white product was recrystallized from dilute ethanol. The m.p. was 167° (dec.). The yield of pure α-oximino-β-phenylpropionic acid was 90%. In subsequent larger runs, it was observed that the oximino acid did not always precipitate from the reaction mixture. However, at the end of the time specified excellent yields were obtained. A modification of the above method was also successful: In a stoppered flask, a solution of 4.0 g. (0.02 mole) of benzylmalonic acid in 25 ml. of ether, 5 ml. of *n*-butyl nitrite (0.04 mole), and 1 ml. of absolute ethanol containing 0.1 g. of HCl (0.0027 mole) was allowed to stand in the refrigerator for about one week. Crystals slowly appeared and the total product after isolation weighed 3 g., an 85% yield of α-oximino-β-phenylpropionic acid.

Following the procedure outlined above, 4.7 g. (0.04 mole) of methylmalonic acid in 25 ml. of ether was nitrosated. After removal of the ether the oily residue was extracted with 10% NaOH, the alkaline extract cooled and acidified. The solution was salted out and exhaustively extracted with ether. Evaporation of the dried ether extract produced a yield of 90% α-oximinopropionic acid, which when crystallized from ether-benzin melted at 180–181° (dec.). Inglis and Knight (54) report 180–181° (dec.)

The nitrosation of 5.3 g. (0.04 mole) of ethylmalonic acid gave 89% yield of α-oximinobutyric acid. The recrystallized acid from ether-benzin melted at 154° (dec.). Hamlin and Hartung (1) report 155° (dec.) corr.

Eight grams (0.05 mole) of *n*-butylmalonic acid gave 87% α-oximino-*n*-caproic acid when nitrosated by Method C. Recrystallized from benzin, the product melted at 136.5° (dec.). The reported value is 137° (dec.) (31).

The nitrosation of 5.6 g. (0.02 mole) of *p*-methoxybenzylmalonic acid was carried out in

50 ml. of ether in the usual manner. A turbidity was produced in 20 minutes. After 35 minutes, the ether was removed and the product recrystallized from dilute alcohol. The yield of product melting at 156° (dec.) was 92%. The reported m.p.'s are 156–157° corr. (1) and 159° (9). This synthesis of the oxime of *p*-methoxyphenylpyruvic acid shows none of the deep red color formation during nitrosation seen when Method A was used (1).

Data on the preparation of α-oximino acids by the three methods described are summarized in Table I. It will be observed that the best yields may be expected from alkylmalonic acids. Furthermore, this method should prove useful in the synthesis of α-oximino-β-(3,4-dialkoxyphenyl)propionic acid, which could not be obtained by nitrosating in sulfuric acid.

TABLE I

α-OXIMINO ACIDS

COMPOUND NITROSATED R = $CH_3CO\underset{R}{C}COOEt$	NITROSATION METHOD*	α-OXIMINO ACID $R{-}\underset{\underset{NOH}{\Vert}}{C}{-}COOH$ R =	Yield, %	M.P. dec. (uncorr.) °C.	Mol. Wt. Calc'd	Neut. Equiv. Found
n-C_4H_9	A	*n*-C_4H_9	86	136	145	145
$C_6H_5CH_2$	A	$C_6H_5CH_2$	85	165	179	180
$C_6H_5CH_2$	A[a]	$C_6H_5CH_2$	52	165		
$C_6H_5CH_2$	B	$C_6H_5CH_2$	62	165		
3,4-$(EtO)_2C_6H_3CH_2$	A	3,4$(EtO)_2C_6H_3CH_2$				
R = $RCH(COOEt)_2$						
C_2H_5	B	C_2H_5	65	154	117	112
n-C_4H_9	B	*n*-C_4H_9	70	135		
$C_6H_5CH_2$	B	$C_6H_5CH_2$	75	165		
R = $RCH(COOH)_2$						
CH_3	C	CH_3	90	180-181	103	103
C_2H_5	C	C_2H_5	89	154		
n-C_4H_9	C	*n*-C_4H_9	87	136.5		
$C_6H_5CH_2$	C[b]	$C_6H_5CH_2$	90	167		
p-$(CH_3O)C_6H_4CH_2$	C	*p*-$(CH_3O)C_6H_4CH_2$	92	156	209	208

[a] Method A modified.

[b] Method C modified.

* *Method A:* Nitrosation of ethyl alkylacetoacetates in acid.

Method B: Nitrosation of ethyl alkylacetoacetates and diethyl alkylmalonates under alkaline conditions.

Method C: Nitrosation of alkylmalonic acids.

Neutral equivalents of α-oximino acids. α-Oximino acids behave like monobasic acids on titration with standard alkali. An accurately weighed sample of about 0.3 g. of α-oximino acid was dissolved in about 40% ethanol and titrated with 0.2 *N* NaOH, using phenolphthalein indicator. Sharp end points were observed and the results are summarized in Table I.

SUMMARY

The synthesis of α-oximino acids has been further studied. It has been found that they may be obtained conveniently and in satisfactory yields by allowing an alkyl nitrite to react with:

1. Ethyl alkylacetoacetates in 85% sulfuric acid if the alkyl group is stable to the concentration of acid employed.

2. Diethyl alkylmalonates in ethanolic sodium ethoxide; ethyl alkylacetoacetates under similar conditions give satisfactory yields of α-oximino acids, but not so high as the corresponding malonic esters.

3. Alkylmalonic acids, in ether solution, in the presence of hydrogen chloride; this method appears to be sufficiently mild for the synthesis of intermediates for the preparation of nuclear-substituted phenylalanines.

4. It was observed that α-oximino acids behave like monobasic acids on titration with alkali and phenolphthalein.

BALTIMORE 1, MD.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

α-ALKOXIMINO ACIDS[1]

KENNETH L. WATERS[2] AND WALTER H. HARTUNG

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The ease with which α-oximino acids may be synthesized and by simple hydrogenation converted into the corresponding α-amino acids (1, 2, 3) raises the question whether they may also be employed in the formation of the peptide linkage. An ideal intermediate would be the acid halide of the oximino acid, RC(=NOH)COCl, but compounds of such type are not described and attempts to prepare them in these laboratories have been unsuccessful. It was thought, however, that the oximino group might be readily removed to form the α-keto acid, from which the amide with an amino acid might be synthesized, RCOCONHCHR′COOH; this through reoximination, RC(=NOH)CONHCHR′COOH, would then serve as a suitable intermediate for peptide synthesis. Unfortunately, not all α-ketoximino acids are easily hydrolyzed by methods that work so well for the hydrolysis of simple oximes.

It has been noted (4) that if oximes of the α-keto acids are heated with dilute mineral acids, they lose carbon dioxide and water, forming nitriles with one less carbon atom. We have verified this observation and have found that the α-oximino acids are also resistant to alkaline hydrolysis. Bouveault and Locquin (5) report the hydrolysis of these acids through the use of 85% formic acid and lead-chamber crystals; many variations of this procedure have been reported in the literature. The procedures are cumbersome and not applicable to the hydrolysis of all α-oximino acids (6).

In attempting to obtain α-keto-β-phenylpropionic acid from the corresponding oxime we tried the usual methods described in standard texts and also procedures which recently have been reported to be successful in the hydrolysis of oximes (7, 8, 9); all of these were unsuccessful when applied to the α-oximino acid. The unsuccessful attempt to reduce an α-oximino acid to an α-imino acid, RC(=NH)COOH, has already been described (10).

Since we were unsuccessful in preparing the α-keto acids, it appeared logical that other derivatives might serve our purposes. In 1938, Adkins and Reeve (11) reported an interesting synthesis of threonine by the catalytic reduction of the O-ethyl ether of oximinoacetoacetic ester. If alkylation should protect the oximino group, permitting the synthesis of an acid chloride derivative which could be coupled with an amino acid, subsequent reduction should give the amino group, thus forming a dipeptide. The equations are:

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[1] Paper No. 7 on syntheses of amino acids. For No. 6, see Barry and Hartung (2).

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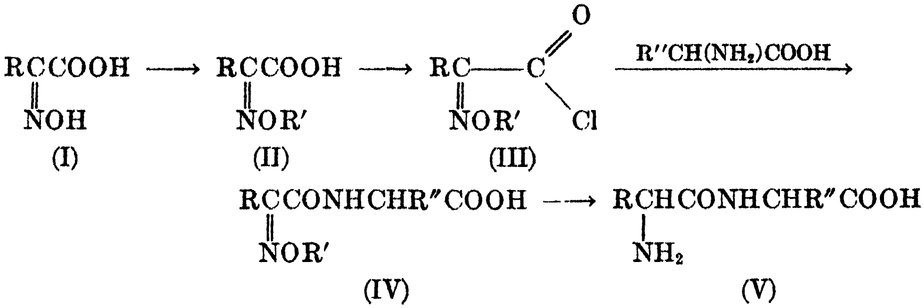

$$\underset{\text{(I)}}{\underset{\substack{\| \\ \text{NOH}}}{\text{RCCOOH}}} \longrightarrow \underset{\text{(II)}}{\underset{\substack{\| \\ \text{NOR}'}}{\text{RCCOOH}}} \longrightarrow \underset{\text{(III)}}{\underset{\substack{\| \\ \text{NOR}'}}{\text{RC}}\!-\!\text{C}\!\overset{\text{O}}{\underset{\text{Cl}}{\lessgtr}}} \xrightarrow{\text{R}''\text{CH(NH}_2\text{)COOH}}$$

$$\underset{\text{(IV)}}{\underset{\substack{\| \\ \text{NOR}'}}{\text{RCCONHCHR}''\text{COOH}}} \longrightarrow \underset{\text{(V)}}{\underset{\substack{| \\ \text{NH}_2}}{\text{RCHCONHCHR}''\text{COOH}}}$$

α-Alkoximino acids are new compounds, and therefore a method for their synthesis is given and several members of this series, along with derivatives, are described. During the course of this investigation three ethoximino (Type II, R′ = Et) and two benzyloximino acids (Type II, R′ = $C_6H_5CH_2$) were prepared. Three of these acids were converted into their corresponding acid chlorides (Type III, two where R′ = Et and one where R′ = $C_6H_5CH_2$). Although the preparation of compounds of Type IV was not attempted, the fact that amides will be formed is proved through the preparation of three corresponding anilides (two where R′ = Et and one where R′ = $C_6H_5CH_2$). Reduction studies on compounds of Type II have shown that catalytic reduction to the amino group may be accomplished.

The preparation of the α-ethoximino acids was accomplished by ethylation with diethyl sulfate in a slightly alkaline medium in the presence of acetone. The three acids which were prepared were low-melting solids which could be purified by distillation under diminished pressure. Preliminary hydrogenation studies on these acids indicated that they would be somewhat difficult to reduce at room temperature and at atmospheric pressure (conditions which would be very desirable if the compounds are to be of value in the preparation of optically active peptides). Since reductive debenzylation of certain types of compounds is very successful, it was thought that it might be preferable to prepare the α-benzyloximino acids. It was found that essentially the same procedure as that employed in the ethylation of the α-oximino acids could be used in the benzylation, benzyl chloride being used as the alkylating agent. Two α-benzyloximino acids were prepared in yields of 42% and 56% respectively; it is believed that the yields will approach the yield of the α-ethoximino acids if the mode of isolation is improved. Preliminary hydrogenation studies have shown that the α-benzyloximino acids may be reduced at room temperature and at two atmospheres pressure.

EXPERIMENTAL

Preparation of the α-oximino acids. The α-oximino acids used in these experiments were prepared by either of two procedures: (a) From the substituted acetoacetic ester in 85% sulfuric acid by the action of alkyl nitrite as described by Hamlin and Hartung (1); (b) from the substituted malonic ester by the action of alkyl nitrite and hydrogen chloride using ether as the solvent as described by Barry (2).

β-Phenyl-α-ethoximinopropionic acid. One-tenth mole, 17.9 g., of β-phenyl-α-oximinopropionic acid in a 500-ml. three-neck flask was dissolved in 100 ml. of 5% aqueous sodium hydroxide and 50 ml. of acetone. The flask was equipped with a mechanical stirrer and two burettes so arranged that a solution of sodium hydroxide and diethyl sulfate could be added simultaneously; a total of 100 ml. of diethyl sulfate and 100 ml. of sodium hydroxide solution (30.5 g. per 100 ml. of solution) was added. The rate of addition after the initial addition of 10 ml. of the sodium hydroxide was such that one drop of alkali was added per drop of diethyl sulfate. Since the concentration of the alkali solution was such that one ml. of alkali would neutralize the acid formed during the hydrolysis of one ml. of diethyl sulfate, the mixture was slightly alkaline throughout the ethylation. The addition of the ethylating reagent required about thirty minutes and during this time the temperature of the water-bath was raised to 70°. As a general rule five moles of diethyl sulfate were added per mole of α-oximino acid.

When the addition was completed, the burettes were replaced by a reflux condenser and the temperature of the bath was raised to boiling. The mixture was refluxed half an hour, after which the reflux condenser was removed and the heating continued about an hour, or until most of the acetone had evaporated, the last traces being removed by suction. The reaction mixture was cooled, made definitely acid to Congo Red with hydrochloric acid, and extracted completely with ether. The combined extracts were washed with several small portions of water, filtered, and dried over sodium sulfate. The solvent was removed and the resulting material distilled at 1 to 2 mm. pressure. The fraction distilling at 115–120° was collected; a yield of 16.3 g., or 79% of β-phenyl-α-ethoximinopropionic acid, was obtained. The colorless crystals melted at 58.5–59°.[3]

Anal. Calc'd for $C_{11}H_{13}NO_3$: N, 6.76; Neutr. equiv. (phenolphthalein), 207.2.
Found: N, 6.59; Neutr. equiv., 209.5.

α-Ethoximinobutyric acid. The ethylation was performed as described above. From 11.7 g. (0.1 mole) of α-oximinobutyric acid, 8.6 g., or 60% of α-ethoximinobutyric acid was obtained. The fraction distilling at 89–95° under 12–14 mm. pressure was collected. When cooled, the product crystallized in long, colorless needles which melted at 61 0–61.5°.

Anal Calc'd for $C_6H_{11}NO_3$: N, 9.65; Neutr. equiv. (phenolphthalein), 145.2.
Found: N, 9.58; Neutr. equiv., 146.5.

α-Ethoximinohexanoic acid. The ethylation was performed as described above. From 29 g. (0.2 mole) of α-oximinohexanoic acid, 28.1 g., or 80% yield of α-ethoximinohexanoic acid was obtained. The fraction distilling at 83–88° under 1 to 3 mm. pressure was collected. The product was a clear liquid which on standing in an ice-bath solidified to long, colorless needles melting at 23°.

Anal. Calc'd for $C_8H_{15}NO_3$: N, 8.09; Neutr. equiv. (phenolphthalein), 173.2.
Found: N, 7.88; Neutr. equiv., 174.0.

β-Phenyl-α-benzyloximinopropionic acid. The benzylation of β-phenyl-α-oximinopropionic acid was accomplished in a manner similar to that described for the ethylation. Nine grams of β-phenyl-α-oximinopropionic acid was treated with five equivalents of benzyl chloride; the sodium hydroxide solution used for the neutralization of the liberated hydrochloric acid had a concentration of 34.7 g. per 100 ml. After the removal of the last traces of acetone, the alkaline benzylating mixture was extracted with ether to remove the benzyl alcohol. However, the mixture of ether and benzyl alcohol was found to contain the sodium salt of β-phenyl-α-benzyloximinopropionic acid. On evaporation, the mixture left an oily residue of benzyl alcohol and the salt; the benzyl alcohol was removed by adding small portions of cold absolute ether and decanting the solvent. When dried, 10.3 g. of the sodium salt of β-phenyl-α-benzyloximinopropionic acid remained. A solution of the salt in water was acidified and the precipitated acid was filtered and recrystallized from ethyl alcohol. A yield of 7.5 g. or 56% of β-phenyl-α-benzyloximinopropionic acid, was obtained as colorless crystals melting at 79–80°.

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[3] All melting points are corrected.

Anal. Calc'd for $C_{16}H_{15}NO_3$: N, 5.20; Neutr. equiv. (phenolphthalein), 269.
Found: N, 5.13; Neutr. equiv., 272.

α-Benzyloximinohexanoic acid. The benzylation was performed and the product isolated as described above. From 7.2 g. of α-oximinohexanoic acid, 4.8 g., or 42% of α-benzyloximinohexanoic acid was obtained. The colorless crystals melted at 61.0–61.5°.

Anal. Calc'd for $C_{13}H_{17}NO_3$: N, 5.95; Neutr. equiv. (phenolphthalein), 235.3.
Found: N, 5.87; Neutr. equiv., 236.

β-Phenyl-α-ethoximinopropionyl chloride. To 6.6 g. of β-phenyl-α-ethoximinopropionic acid was added 6.6 g. (4 ml.) of thionyl chloride. The mixture was refluxed for half an hour; during this time the condenser was protected from moisture by a calcium chloride tube. To remove the excess thionyl chloride and the liberated hydrogen chloride, two 50-ml. portions of dry benzene were added and each removed under reduced pressure. The product was distilled under 1 to 2 mm. pressure and the fraction distilling at 95–97° was collected. A yield of 6.0 g., or 85% of β-phenyl-α-ethoximinopropionyl chloride was obtained.

Anal. Calc'd for $C_{11}H_{12}ClNO_2$: N, 6.21; Cl, 15.72.
Found: N, 6.04; Cl, 15.61.

α-Ethoximinohexanoyl chloride. To 10 g. of α-ethoximinohexanoic acid dissolved in 25 ml. of dry benzene was added 9.8 g. (6.0 ml.) of thionyl chloride dissolved in 15 ml. of dry benzene. The mixture was allowed to stand overnight, protected from atmospheric moisture, and then refluxed on the steam-bath for about 20 minutes or until the mixture started to darken. The excess thionyl chloride and liberated hydrogen chloride were removed by the addition of two portions of dry benzene with subsequent distillation under reduced pressure. The product was distilled under 1 to 2 mm. pressure. Seven and eight-tenths grams of α-ethoximinohexanoyl chloride was obtained which distilled between 58° and 63° at 1 to 2 mm. An additional 1.2 g. of material distilling within the range of the original α-ethoximinohexanoic acid (78–83°) was also collected. Allowing for the recovered acid, a yield of 81% of α-ethoximinohexanoyl chloride was obtained.

Anal. Calc'd for $C_8H_{14}ClNO_2$: N, 7.31; Cl, 18.51.
Found: N, 7.30; Cl, 16.1.[4]

β-Phenyl-α-benzyloximinopropionyl chloride. To 5 g. of β-phenyl-α-benzyloximinopropionic acid in 25 ml. of dry benzene was added 6.6 g. (4 ml.) of thionyl chloride in 15 ml. of dry benzene. The mixture was refluxed for two hours with protection from moisture. To remove the excess thionyl chloride and liberated hydrogen chloride, two 50-ml. portions of dry benzene were added and each removed under diminished pressure. The product was distilled under 1 to 2 mm. pressure and the fraction distilling at 170–175° was collected. A yield of 4.7 g., or 88% of β-phenyl-α-benzyloximinopropionyl chloride was obtained.

Anal. Calc'd for $C_{16}H_{14}ClNO_2$: N, 4.87; Cl, 12.34.
Found: N, 4.82; Cl, 12.13.

Ethyl β-phenyl-α-ethoximinopropionate. About 3 g. of β-phenyl-α-ethoximinopropionyl chloride was added to 10 ml. of absolute ethyl alcohol and the mixture refluxed on the steam-bath for half an hour. The excess alcohol was removed under diminished pressure and the product was dissolved in ether. The ethereal solution was washed with several small portions of saturated sodium chloride solution, then dried over sodium sulfate, and filtered into a distilling flask. After removal of the solvent, the product was distilled at 1 to 3 mm. pressure and the fraction distilling at 118–120° was collected. The ethyl β-phenyl-α-ethoximinopropionate so prepared was a clear, colorless liquid.

Anal. Calc'd for $C_{13}H_{17}NO_3$: N, 5.95; sapon. value, 235.3.
Found: N, 5.79; sapon. value, 232.

Ethyl α-ethoximinohexanoate. To 4 g. of α-ethoximinohexanoyl chloride was added 25 ml. of absolute ethyl alcohol and the mixture refluxed on the steam-bath for one hour. The excess alcohol was removed under diminished pressure and the residue dissolved in ether.

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[4] Chlorine analysis unsatisfactory; highest result of several determinations reported.

The ethereal solution was washed with two small portions of saturated sodium chloride solution, dried over sodium sulfate, and filtered into a distilling flask. After the removal of the solvent the ester was distilled at 1 to 3 mm. pressure and the fraction distilling at 60–65° was collected. A yield of 3.7 g., or 88% of ethyl α-ethoximinohexanoate was obtained as a clear colorless liquid.

Anal. Calc'd for $C_{10}H_{19}NO_3$: N, 6.96; sapon. value, 201.3.
Found: N, 6.82; sapon. value, 201.

β-Phenyl-α-ethoximinopropionanilide. To 9.2 g. of crude β-phenyl-α-ethoximinopropionyl chloride (product not distilled but excess thionyl chloride removed under diminished pressure), dissolved in 25 ml. of dry benzene, was added 9.2 g. (9 ml.) of aniline dissolved in 25 ml. of dry benzene. The mixture was refluxed on the steam-bath for half an hour, then cooled, and the precipitated aniline hydrochloride was filtered. The benzene was removed by distillation under reduced pressure and the residue taken up with 20 ml. of absolute ether. To this solution was added 80 ml. of petroleum ether; a light yellow precipitate deposited which was at first thought to be the desired anilide. This product weighed 3.2 g. and on further purification (dissolving in absolute ether and precipitating with petroleum ether) had the constant melting point 88–89°. Nitrogen analysis, neutralization equivalent, and examination of hydrolysis products indicated that it was a salt of aniline and β-phenyl-α-ethoximinopropionic acid which probably resulted through the use of the crude starting material.

β-Phenyl-α-ethoximinopropionanilide was isolated from the ethereal filtrates by evaporating to dryness and purifying the residue by dissolving in ethyl alcohol and precipitating by adding water. A total of 5.8 g. of the anilide was obtained. The colorless crystals melted at 59–60°.

Anal. Calc'd for $C_{17}H_{18}N_2O_2$: N, 9.92. Found: N, 9.84.

α-Ethoximinohexanilide. To 4.2 g. of α-ethoximinohexanoyl chloride, dissolved in 25 ml. of dry benzene, was added 4.2 g. (4.1 ml.) of aniline, dissolved in 15 ml. of dry benzene; the aniline hydrochloride, which formed as a white precipitate, was filtered and the solvent removed under diminished pressure. The product was distilled at 1 to 3 mm. pressure and the fraction distilling at 133–138° was collected. A yield of 4.3 g. (77%) of α-ethoximinohexanilide, was obtained as a slightly yellow, somewhat viscous, liquid, which failed to crystallize on prolonged standing at room temperature.

Anal. Calc'd for $C_{14}H_{20}N_2O_2$: N, 11.28. Found: N, 11.18.

β-Phenyl-α-benzyloximinopropionanilide. To 1.1 g. of β-phenyl-α-benzyloximinopropionyl chloride, dissolved in 25 ml. of absolute ether, was added 0.8 g. of aniline, dissolved in 10 ml. of absolute ether. The mixture was allowed to stand and the precipitated aniline hydrochloride filtered. The solvent was removed under diminished pressure. The product was purified by dissolving in warm 95% ethyl alcohol and precipitating with water. A yield of 1.2 g. (90%) of β-phenyl-α-benzyloximinopropionanilide was obtained as a colorless crystalline substance which melted at 73.5–74°.

Anal. Calc'd for $C_{22}H_{20}N_2O_2$: N, 8.14. Found: N, 8.03.

Hydrogenolysis of the α-alkoximino acids. A thorough investigation of the hydrogenolysis and reduction of the α-alkoximino acids will be made later; however, preliminary experiments show that this class of compounds may be catalytically reduced. Using a prepared palladium charcoal catalyst (12) and acidified ethyl alcohol for the solvent, the reduction of β-phenyl-α-ethoximinopropionic acid was very slow at room temperature and two atmospheres pressure; only about 10% being reduced after about three hours. Raney nickel catalyst was no more satisfactory than the palladium catalyst. The use of Adams' catalyst in methyl and in ethyl alcohol under 2 atmospheres of pressure and at room temperature did not effect a rapid reduction of α-ethoximinohexanoic acid. Several experiments in the catalytic reduction of β-phenyl-α-benzyloximinopropionic acid indicated this compound is more easily reduced than is its ethoxy analog. A fifty per cent yield of amino acid was obtained using a palladium catalyst in glacial acetic acid. It is believed that a systematic study of conditions of hydrogenation will show that the α-alkoximino acids may be catalytically reduced at room temperature and at atmospheric pressure.

SUMMARY

1. A method for the alkylation of the α-oximino acids has been devised and employed successfully.

2. It has been shown that, if the oximino group of the α-oximino acids is protected by alkylation, the corresponding acid chlorides may be prepared in good yields.

3. The acid chlorides of the α-alkoximino acids have been shown to react as characteristic acid chlorides.

4. Preliminary reduction studies indicate that the α-alkoximino acids may be reduced to the corresponding amino acid.

5. It is proposed that the α-alkoximino acids may serve as convenient intermediates in the synthesis of peptides.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

BIOTIN. IX.[1] A SYNTHESIS OF *dl*-DEHYDROBIOTIN

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One of the methods contemplated for the synthesis of biotin called for the preparation of 2-keto-4-(δ-carboxybutyl)-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole (XV), which we have called *dehydrobiotin*.

The transformation of dehydrobiotin into biotin by the addition of a molecule of hydrogen was a problem which would have to be faced when the synthesis of dehydrobiotin had been achieved.

The main purpose in seeking dehydrobiotin as the key intermediate lay in the fact that separation of isomers would be deferred until the final step. Moreover, the fact that the urea bridge was already present in the dehydrobiotin molecule held out the hope that, if reduction could be made to take place, it might yield *cis* isomers exclusively. Since the completion of this work Harris and others (1) have argued, on the basis of resistance to hydrolysis, that biotin probably has the *cis* configuration with respect to the nitrogen atoms.

In addition to the above reasons, it was of interest to find out whether or not dehydrobiotin itself possessed any biotin-like activity.

The present paper reports the total synthesis of *dl*-dehydrobiotin.

In the following paper in this series the synthesis of a model compound, 2-keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole, will be presented.

The starting material, 7-carbethoxy-2-heptenoic acid (I) (2), was treated with mercuric acetate in methanol, utilizing the excellent procedure of Carter and others (3) for the preparation of serine and threonine. The crystalline addition product [probably 2-acetoxymercuri-3-methoxy-7-carbethoxy-heptanoic acid (II)] was brominated with bromine dissolved in aqueous potassium bromide solution to give 2-bromo-3-methoxy-7-carbethoxyheptanoic acid (III) as an oily mixture of the two racemates. The latter was hydrolyzed in the cold with alkali to give 2-bromo-3-methoxysuberic acid (IV) in the form of an oil which was probably a mixture of the two possible racemates. The yield of IV from I was 72%.

Treatment of the bromo acid IV with ammonia at 100° gave 2-amino-3-methoxysuberic acid (V) of which 36% was isolated as a pure crystalline isomer. In addition, there was present in the mother liquor at least an equal amount of V which could be used in subsequent transformations. The amino acid V was benzoylated by the Schotten-Baumann method to give a 97% yield of 2-benzamido-3-methoxysuberic acid (VI) which upon treatment with benzoyl chloride

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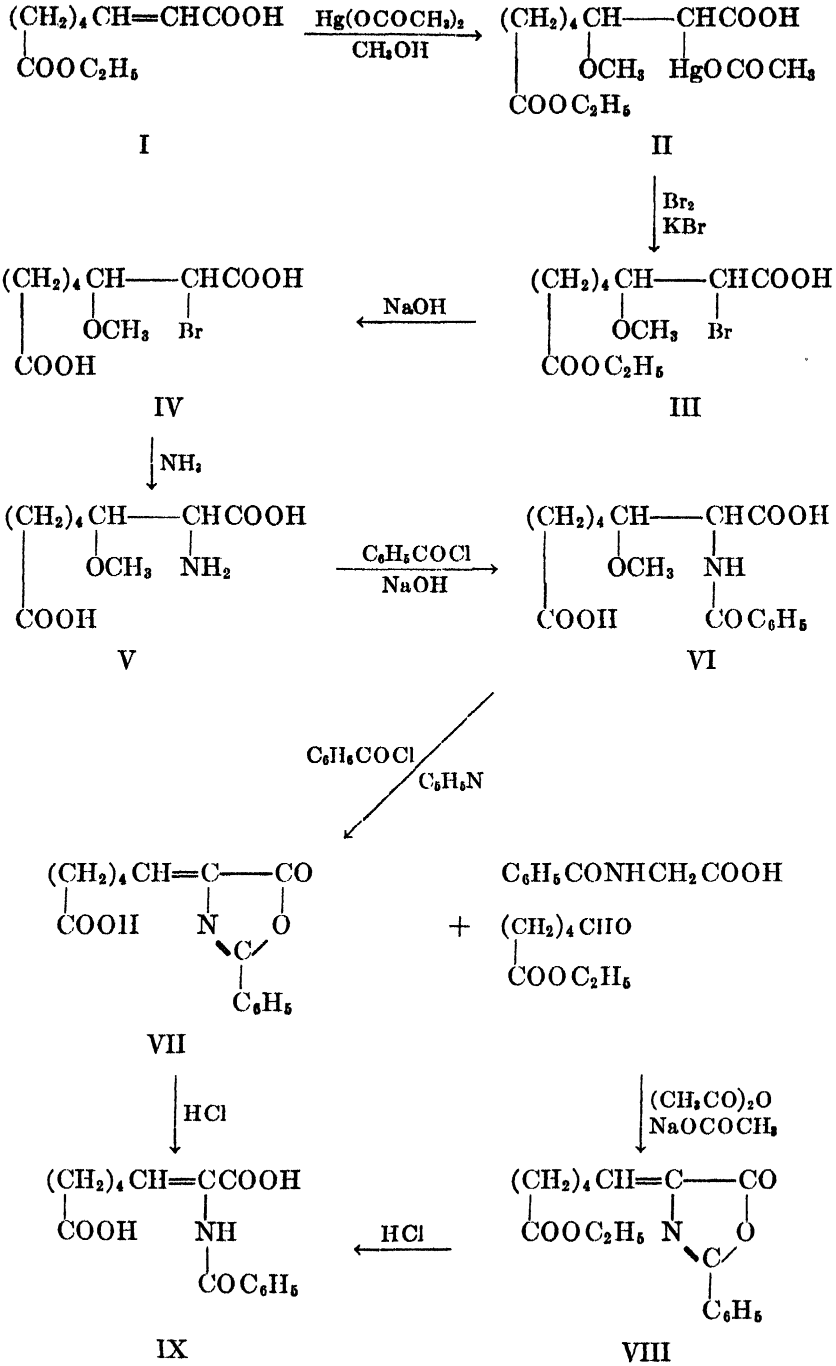
[1] Paper VIII in this series is to be found in *J. Org. Chem.*, **12**, 328 (1947).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NH₃
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VI
C₆H₅COCl
C₅H₅N
VII
C₆H₅CONHCH₂COOH
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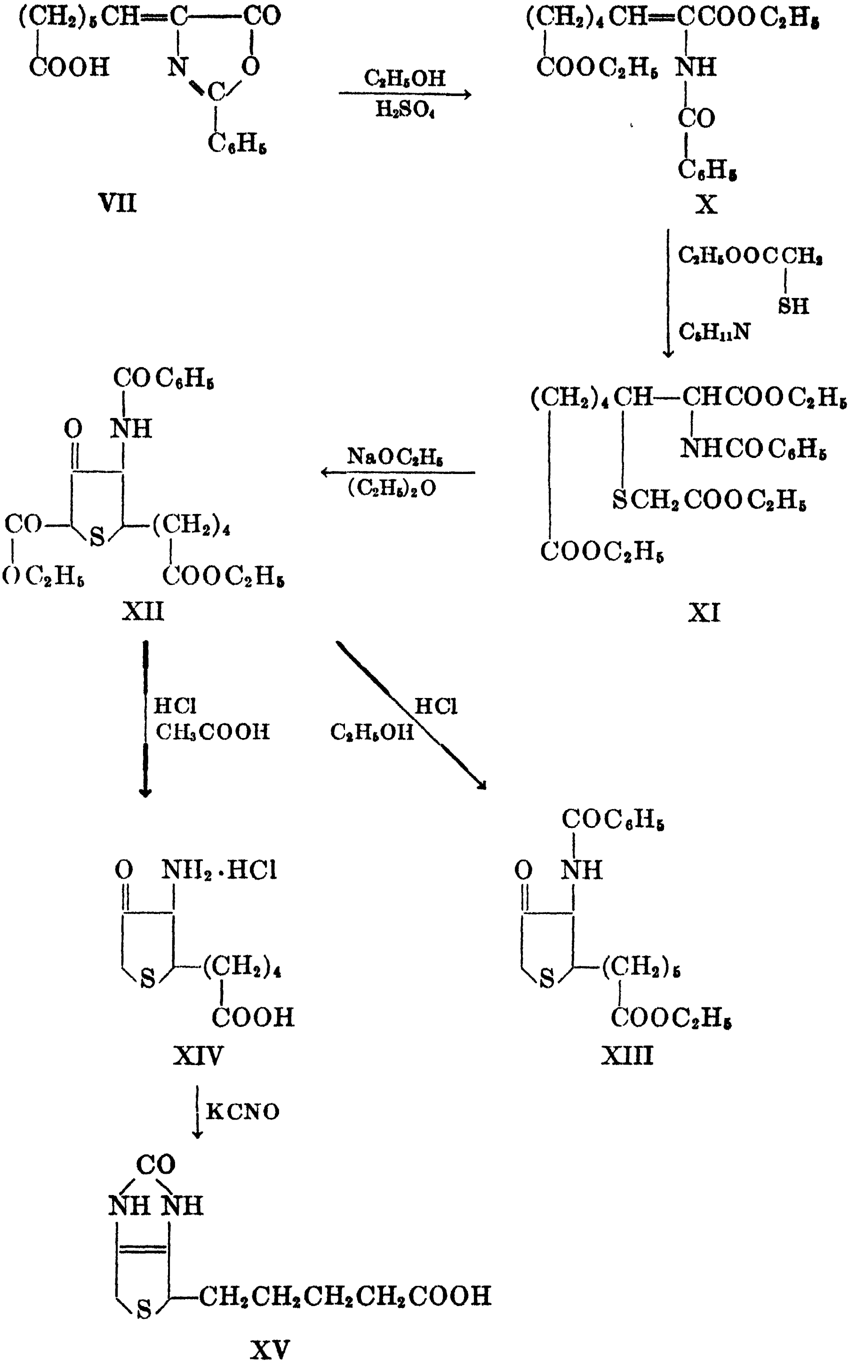
IX


VII
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CH3COOH
HCl
C2H5OH
XIV
XIII
KCNO
XV

and pyridine yielded the azlactone VII[2] mixed with benzoic acid. The crude mixture was esterified with ethanol and sulfuric acid and gave, after the removal of ethyl benzoate, 70% of ethyl 2-benzamido-7-carbethoxy-2-heptenoate (X).

The free acid IX corresponding to X was obtained in a pure, crystalline form from the interaction of ethyl δ-formylvalerate with hippuric acid followed by acid hydrolysis. IX was also obtained from an acid hydrolysis of the crude azlactone VII.

The addition of ethyl thioglycolate to X took place in the presence of piperidine to give ethyl 2-benzamido-3-(carbethoxymethylthio)suberate (XI) in the form of an oil. The latter was found to undergo the Dieckmann reaction in the presence of sodium ethoxide and dry ether to give a crystalline sodium salt which on acidification yielded 2-(δ-carbethoxybutyl)-3-benzamido-4-keto-5-carbethoxythiophane (XII). The latter was obtained as an oil in 17% yield from X and was characterized as the 2,4-dinitrophenylhydrazone. The keto ester XII and its sodium salt give a dark green color with alcoholic ferric chloride.

Hydrolysis of XII with a mixture of alcohol and 12 *N* hydrochloric acid led to stripping of the 5-carbethoxy group and gave 2-(δ-carbethoxybutyl)-3-benzamido-4-ketothiophane (XIII) which was characterized as the phenylhydrazone and as the 2,4-dinitrophenylhydrazone.

More drastic hydrolysis of XII, with a mixture of acetic and hydrochloric acids, stripped the benzoyl group and the ester group of the side-chain as well as the 5-carbethoxy group, to give 2-(δ-carboxybutyl)-3-amino-4-ketothiophane hydrochloride (XIV). The latter substance upon treatment with potassium cyanate in water yielded *dl*-dehydrobiotin (XV). The yield of pure XV from XII was 28%.

Dehydrobiotin was found to be biologically inactive with *L. casei*.

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EXPERIMENTAL

2-Bromo-3-methoxysuberic acid (IV). A solution prepared from 20 g. of 7-carbethoxy-2-heptenoic acid (2), 31.9 g. of mercuric acetate, and 190 cc. of methanol was shaken at room temperature for two days. The white, crystalline addition product (II) was filtered, washed with methanol, and air-dried; yield 37.6 g.

To a cold (5°), gently stirred solution of 37.6 g. of II and 17.9 g. of potassium bromide in 100 cc. of water was added, dropwise, during the course of one hour, a solution composed of 16 g. of bromine, 17.9 g. of potassium bromide, and 35 cc. of water. The reaction was carried out in an open beaker illuminated with a 200-watt photoflood lamp. The mixture was stirred an additional fifteen minutes, the slight excess of bromine was removed with sodium bisulfite, the solution was shaken once with ether, and the aqueous layer was acidified to *p*H 1–2. The mixture was extracted with ether, the ether solution was washed with saturated salt solution, dried with magnesium sulfate, and evaporated to dryness. A nearly colorless oil composed of III was obtained; yield 23.3 g.

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[2] The lability of a β-hydroxy group under azlactonizing conditions was discovered by Erlenmeyer, Jr. and Frühstück (4) in the conversion of β-phenylserine into the azlactone of α-acetamidocinnamic acid. Carter *et al.* (5) showed that methoxy and acetoxy groups were also labile. Thus N-benzoyl-*dl*-allothreonine, N-benzoyl-O-methyl-*dl*-threonine, and N-benzoyl-O-acetyl-*dl*-allothreonine all were found by Carter's group to give the same azlactone upon treatment with benzoyl chloride and pyridine.

A stirred mixture of 6.2 g. of III and 8.4 cc. of 0.5 *N* alkali was cooled to 15–20° and treated during thirty-five minutes with 8.4 cc. of 5 *N* alkali. The mixture was stirred an additional fifty minutes at 25°, washed once with ether, and acidified. The solution was saturated with salt and extracted with ether. The ether solution was washed with saturated salt solution, dried, and the solvent was evaporated. The resulting 2-bromo-3-methoxysuberic acid (IV) was obtained as a colorless oil; yield 5.4 g.

Anal. Calc'd for $C_9H_{15}BrO_5$: C, 38.2; H, 5.3; neutr. equiv., 142.
Found: C, 38.6; H, 5.6; neutr. equiv., 146.

It is very probable that IV is a mixture of the two theoretically possible racemates.

2-Amino-3-methoxysuberic acid (V). A solution of 56 g. IV in 600 cc. of 28% ammonia was heated in a glass-lined autoclave for six hours at 100°. The solution was treated with Norit, filtered, and the filtrate was evaporated to dryness *in vacuo*. The gummy residue was dissolved in water and the solution was again evaporated to dryness *in vacuo*. This process was repeated twice more. Finally, the residue was slurried in water and filtered. The yield of crystalline, nearly white amino acid V was 15.4 g. (36%), m.p. 235–237° (dec.). After one recrystallization from water the m.p. was unchanged.

Anal. Calc'd for $C_9H_{17}NO_5$: C, 49.3; H, 7.8; N, 6.4.
Found: C, 49.2; H, 6.9; N, 6.4.

The mother liquor remaining after filtration of the crystalline amino acid was found to contain at least an equal amount of V (probably a mixture of racemates). This could be utilized by acidifying the solution to *p*H 3, evaporating to dryness, and benzoylating the resulting crude residue.

2-Benzamido-3-methoxysuberic acid (VI). To an ice-cold, stirred solution of 2.8 g. of V in 25.6 cc. of *N* alkali was added, alternately, during one-half hour, 3.6 g. of benzoyl chloride and 38.4 cc. of *N* alkali. After being stirred for an additional fifteen minutes, the mixture was acidified and extracted with ether. The ether solution was dried with magnesium sulfate and evaporated to dryness. The gummy residue was leached three times with hot petroleum ether (b.p. 90–100°). The residual colorless gum consisted of 4.0 g. of nearly pure VI.

Anal. Calc'd for $C_{16}H_{21}NO_6$: C, 59.5; H, 6.5; N, 4.3.
Found: C, 58.8; H, 6.5; N, 4.8.

Ethyl 2-benzamido-7-carbethoxy-2-heptenoate (X). To an ice-cold solution of 10.1 g. of VI in 75 cc. of dry pyridine was added, with swirling, 8.8 g. of benzoyl chloride. After fifteen minutes at 0° the mixture was poured into cold, dilute hydrochloric acid containing 100 cc. of the 12 *N* acid. The mixture was saturated with salt and extracted with ether. The ether layer was washed with dilute hydrochloric acid, then with saturated salt solution, dried with magnesium sulfate, and evaporated to dryness. The residue, 15.6 g., consisted of a mixture of the *azlactone of 2-benzamido-7-carboxy-2-heptenoic acid (VII)* and benzoic acid.

The crude product was dissolved in 100 cc. of dry ethanol containing 5 cc. of sulfuric acid, 100 cc. of benzene was added, and the whole was refluxed sixteen hours in a Soxhlet apparatus containing magnesium sulfate in the thimble. The resulting solution was cooled, diluted with an equal volume of water, the mixture was saturated with salt and extracted with ether. The ether solution was washed in succession with water, bicarbonate solution, and finally with water. After drying, the solution was evaporated *in vacuo*. In order to remove the ethyl benzoate, the residual oil was distilled from a water-bath at 80°/0.5 mm. The product (X) was obtained as a light yellow oil remaining in the distillation flask; yield 7.7 g. (70% from VI).

Anal. Calc'd for $C_{19}H_{25}NO_5$: C, 65.7; H, 7.2; N, 4.0.
Found: C, 64.4; H, 7.4; N, 3.5.

2-Benzamido-7-carboxy-2-heptenoic acid (IX). A number of experiments were performed on the condensation of ethyl δ-formylvalerate (2) with hippuric acid to form the *azlactone of 2-benzamido-7-carbethoxy-2-heptenoic acid (VIII)*. The crude products were then subjected to acid hydrolysis and, in the following procedure, an 8% yield of IX was obtained.

A mixture of 24.6 g. of freshly distilled ethyl δ-formylvalerate, 21.4 g. of hippuric acid, 55 g. of acetic anhydride, and 9.8 g. of anhydrous sodium acetate was stirred vigorously at 55° for five and one-quarter hours. The resulting, nearly clear, orange solution was poured into cold water. The mixture was extracted with ether and the ether solution was evaporated to dryness *in vacuo*, the bath temperature being finally raised to 85°. The residue was a light brown oil consisting of 39.9 g. of impure VIII. A mixture of 5 g. of the latter, 100 cc. of 3-A alcohol, and 200 cc. of 2 *N* hydrochloric acid was refluxed one-quarter hour, then concentrated *in vacuo* to 50–60 cc. The clear solution was decanted from the gum, and on cooling and standing 348 mg. (8%) of IX separated in the form of colorless crystals; m.p. 187–188°. The m.p. was unchanged after one recrystallization from water. A mixture of IX and hippuric acid (m.p. 187–188°) melted at 165–175°.

Anal. Calc'd for $C_{15}H_{17}NO_5$: C, 61.8; H, 5.8; N, 4.8; neutr. equiv., 146.
Found: C, 62.1; H, 5.6; N, 4.6; neutr. equiv., 146.

Similarly, acid hydrolysis of the crude mixture of azlactone VII and benzoic acid obtained from the reaction of VI with benzoyl chloride and pyridine gave an acid identical in m.p. and mixed m.p. with IX.

The independent synthesis of IX by the two described methods confirms the presence of the azlactone structures assigned to VII and VIII.

Ethyl 2-benzamido-3-(carbethoxymethylthio)suberate (XI). A mixture of 101 g. of X, 42 g. of ethyl thioglycolate, and 250 cc. of dry ethanol was treated with 2 cc. of piperidine. The mixture was kept at 25° for seventeen hours, then refluxed seven hours. The solution was evaporated to dryness *in vacuo*, the resulting oil was dissolved in ether, the ether solution was cooled to 0° and washed in succession with ice-cold *N* alkali and saturated salt solution, dried with magnesium sulfate, and evaporated to dryness. The yield of XI was 90 g.

Anal. Calc'd for $C_{23}H_{33}NO_7S$: C, 59.1; H, 7.1; N, 3.0.
Found: C, 58.2; H, 6.9; N, 3.0.

2-(δ-Carbethoxybutyl)-3-benzamido-4-keto-5-carbethoxythiophane (XII). The sodium ethoxide obtained by evaporation of a solution of 9 g. sodium in absolute ethanol followed by baking *in vacuo* at 125–130° was suspended in 300 cc. of dry ether and a solution of 90 g. of XI in 600 cc. of ether was admitted, with cooling, under a nitrogen atmosphere. The stoppered flask was shaken at room temperature for one day and the contents were poured into iced water. The crystalline sodium salt was filtered, washed with water and ether, and then added with stirring to cold, dilute excess acetic acid. The mixture was extracted with ether, the ether layer was washed thoroughly with sodium bicarbonate solution followed by saturated salt solution, dried, and evaporated to dryness *in vacuo*. The residue consisted of 20.6 g. (17% from X) of the keto ester XII in the form of a very light yellow oil.

Anal. Calc'd for $C_{21}H_{27}NO_6S$: C, 59.7; H, 6.4; N, 3.3.
Found: C, 59.4; H, 7.0; N, 3.3.

XII and the sodium salt of XII give a dark green color on treatment with alcoholic ferric chloride.

The *2,4-dinitrophenylhydrazone* separates in lemon-yellow needles from a solution of XII in 2,4-dinitrophenylhydrazine reagent (prepared by dissolving 2 g. of the hydrazine in 300 cc. of 3-A alcohol and 25 cc. of 12 *N* hydrochloric acid). The m.p. after one recrystallization from benzene-alcohol was 191–192° (dec.).

Anal. Calc'd for $C_{27}H_{31}N_5O_9S$: C, 53.9; H, 5.2; N, 11.7.
Found: C, 53.8; H, 5.0; N, 11.4.

2-(δ-Carbethoxybutyl)-3-benzamido-4-ketothiophane (XIII). A mixture of 1.4 g. of XII, 17 cc. of 3-A alcohol, and 14 cc. of 12 *N* hydrochloric acid was refluxed forty minutes; 3 cc. of alcohol and 2 cc. of 12 *N* hydrochloric acid were added and the mixture was refluxed an additional five minutes. An equal volume of water was added, the mixture was saturated with salt and extracted with ether. The ether layer was washed with saturated salt solution until the washings were neutral, dried, and evaporated. The ketone XIII was obtained as a light yellow oil; yield 0.85 g.

Anal. Calc'd for $C_{18}H_{23}NO_4S$: C, 61.9; H, 6.6; N, 4.0.
Found: C, 62.0; H, 6.5; N, 3.2.

In contrast to XII, XIII gives a negative color reaction with alcoholic ferric chloride.

The *2,4-dinitrophenylhydrazone* separates in yellow needles from an ice-cold solution of 2,4-dinitrophenylhydrazine in alcoholic-hydrochloric acid; m.p. 168–170°. The m.p. was unchanged after one recrystallization from 3-A alcohol.

Anal. Calc'd for $C_{24}H_{27}N_5O_7S$: C, 54.4; H, 5.1; N, 13.2.
Found: C, 54.0; H, 5.0; N, 13.3.

The *phenylhydrazone* of XIII separates as colorless crystals from 60% alcohol; m.p. 145–147°.

Anal. Calc'd for $C_{24}H_{29}N_3O_3S$: C, 65.6; H, 6.6; N, 9.6.
Found: C, 65.7; H, 7.3; N, 9.8.

2-Keto-4-(δ-carboxybutyl)-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole (dl-dehydrobiotin) (XV). A mixture of 3.1 g. of XII, 20 cc. of acetic acid, and 20 cc. of 6 *N* hydrochloric acid was refluxed five and one-half hours. During the first three hours 20 cc. of 12 *N* hydrochloric acid was added in five portions. The mixture was cooled to 5° and filtered from benzoic acid. The filtrate was diluted with an equal volume of water and extracted thoroughly with ether. The aqueous solution was evaporated to dryness *in vacuo*, the light brown crystalline residue was dissolved in 30 cc. water, treated with Norit, filtered, and the filtrate was evaporated to dryness. The residue consisted of 1.1 g. of crude *2-(δ-carboxybutyl)-3-amino-4-ketothiophane hydrochloride (XIV).* The latter was dissolved in 10 cc. of water, the solution was treated with Norit and filtered. To the filtrate was added a solution of 0.7 g. of potassium cyanate in 5 cc. of water. The nearly colorless solid which separated was filtered and washed with a small amount of cold water; yield 700 mg.; m.p. 168–170°. One recrystallization from water gave 491 mg. (28% from XII) of dehydrobiotin as colorless crystals, m.p. 175–176°. The m.p. was not raised upon further recrystallizations.

Anal. Calc'd for $C_{10}H_{14}N_2O_3S$: C, 49.6; H, 5.8; N, 11.6; S, 13.2.
Found: C, 49.8; H, 5.5; N, 11.3; S, 13.4.

Dehydrobiotin is relatively insoluble in cold water, quite soluble in hot water, and soluble in sodium bicarbonate solution.

The *methyl ester* was obtained by refluxing a mixture of 0.5 g. of XV, 60 cc. of methanol, 60 cc. of chloroform, and 0.5 cc. of sulfuric acid seven hours in a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. The mixture was diluted with water, the chloroform layer was separated and washed with bicarbonate solution followed by water, dried and evaporated to dryness *in vacuo*. The residue, upon recrystallization from water gave 200 mg. colorless crystals, m.p. 123–124°.

Anal. Calc'd for $C_{11}H_{16}N_2O_3S$: C, 51.6; H, 6.3; N, 10.9.
Found: C, 51.8; H, 6.2; N, 10.7.

SUMMARY

Addition of ethyl thioglycolate to ethyl 2-benzamido-7-carbethoxy-2-heptenoate and Dieckmann cyclization of the resultant adduct gives 2-(δ-carbethoxybutyl)-3-benzamido-4-keto-5-carbethoxythiophane. Drastic acid hydrolysis of the latter forms 2-(δ-carboxybutyl)-3-amino-4-ketothiophane hydrochloride,

which, on treatment with potassium cyanate, is readily converted to *dl*-dehydrobiotin.

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[Contribution from the Department of Biochemistry, Cornell Medical College and from the Lederle Laboratories Division, American Cyanamid Company]

BIOTIN. X. SYNTHESIS OF *dl*-2-KETO-4-METHYL-2,3,4,6-TETRAHYDRO-1-THIENO[3,4]IMIDAZOLE

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The synthesis of *dl*-dehydrobiotin was described in paper IX of this series (1). Before the synthesis was undertaken, however, it was thought advisable to investigate the reactions on a model substance, 2-keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole (V), in order to determine the feasibility for the preparation of dehydrobiotin.

The starting material, the azlactone of α-benzamidocrotonic acid (I) has been prepared by Carter and others (2) from the reaction between N-benzoylthreonine and derivatives and benzoyl chloride, and by the condensation of acetaldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate. Although the first method gives good yields it is rather long. In the second method it has now been found possible by slightly modifying the procedure of Carter and co-workers to increase the yield from 18–21% to 47%.

When the azlactone I was treated with ethyl thioglycolate and absolute ethanol in the presence of piperidine, the mercaptan added to the α,β-double bond, the azlactone ring opened and the carboxyl group was esterified; this gave in one step 76% of ethyl α-benzamido-β-carbethoxymethylthiobutyrate (II) as an oil.[1]

The thioether II was found to undergo the Dieckmann reaction in the presence of sodium ethoxide and ether to give 2-methyl-3-benzamido-4-keto-5-carbethoxythiophane (III) in 31% yield as a gum. The β-keto ester III gave a green color with an alcoholic solution of ferric chloride and was characterized as the 2,4-dinitrophenylhydrazone.

When III was refluxed with a mixture of acetic and hydrochloric acids the carbethoxyl and N-benzoyl groups were eliminated. From the reaction mixture were isolated crystals of 2-methyl-3-amino-4-ketothiophane hydrochloride (IV) which, without further purification, upon treatment with potassium cyanate in water, deposited crystals of 2-keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]-imidazole (V). The yield of V was 16% from III.

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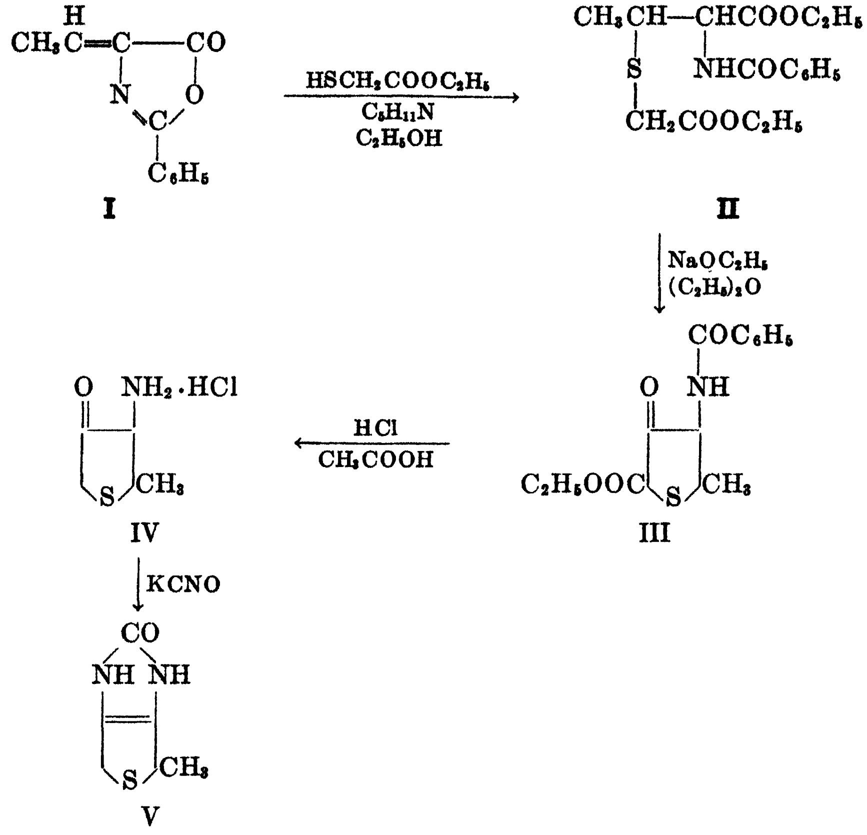
[1] Similar reactions have been reported in the literature. Nicolet (3) treated the azlactone of α-benzamidocinnamic acid with *p*-tolylmercaptan and ethanol in the presence of sodium ethoxide and obtained ethyl α-benzamido-β-(*p*-tolylmercapto)-β-phenylpropionate. More recently, Carter and others (4) added benzylmercaptan and methanol to the azlactone I in the presence of sodium methoxide and obtained methyl α-benzamido-β-benzylmercaptobutyrate.



EXPERIMENTAL

Azlactone of α-benzamidocrotonic acid (I). The following modification of the procedure of Carter and co-workers (2) was found to produce the best results: To a stirred, 25° mixture of 35.8 g. of hippuric acid, 16.4 g. of anhydrous sodium acetate and 100 cc. of acetic anhydride was added, during one-half hour, 100 cc. of freshly distilled acetaldehyde. The mixture was then warmed to 60° and stirred continuously for eleven hours, whereupon it was poured into ice and water. The resulting solid was filtered and washed with water. The crude wet azlactone was dissolved in the minimum amount of warm ether, the water layer was removed, the ether solution was dried with magnesium sulfate, filtered, and the filtrate was cooled in a dry-ice-acetone bath. The azlactone separated as nearly colorless crystals. After one more recrystallization from ether, 17.6 g. (47%) of practically pure I was obtained; m.p. 88–91°.

Ethyl α-benzamido-β-carbethoxymethylthiobutyrate (II). A solution of 12.7 g. of I and 8.2 cc. of ethyl thioglycolate in 100 cc. of ethanol was treated with five drops of piperidine, allowed to stand at 25° for three days, then refluxed seventy-five minutes, and finally evaporated to dryness at 50°/1 mm. The residual light brown oil was dissolved in ether, washed five times with ice-cold 10% sodium bicarbonate solution, three times with saturated salt solution, dried with magnesium sulfate, and evaporated to dryness. The yield of II as a light brown oil was 18.2 g. (76%).

Anal. Calc'd for $C_{17}H_{23}NO_5S$: C, 57.8; H, 6.5; N, 4.0.
Found: C, 58.5; H, 5.6; N, 4.5.

2-Methyl-3-benzamido-4-keto-5-carbethoxythiophane (III). A mixture of sodium ethoxide prepared from 0.59 g. of sodium, 4.5 g. of II, and 150 cc. of dry ether was shaken at 5° for two hours and at room temperature for sixteen hours. The mixture was cooled to 5° and extracted with several portions of iced water. The aqueous extracts were acidified as rapidly as possible with cold, dilute acetic acid. The resulting emulsion was saturated with salt and extracted with ether. The ether solution was washed with cold 10% bicarbonate solution followed by saturated salt solution, dried with magnesium sulfate, treated with Norit, filtered, and the filtrate was evaporated to dryness. The keto ester III was obtained as an amber oil; yield 1.2 g. (31%).

Anal. Calc'd for $C_{15}H_{17}NO_4S$: C, 58.7; H, 5.5; N, 4.6.
Found: C, 58.5; H, 6.6; N, 4.4.

The keto ester gives a green color with alcoholic ferric chloride, is soluble in cold, dilute alkali, and forms a *2,4-dinitrophenylhydrazone* upon treatment in alcohol with a solution of 2,4-dinitrophenylhydrazine in alcohol and hydrochloric acid. The m.p. of the dinitrophenylhydrazone is 210–213°.

Anal. Calc'd for $C_{21}H_{21}N_5O_7S$: C, 51.8; H, 4.3; N, 14.4.
Found: C, 52.0; H, 4.2; N, 14.6.

2-Keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole (V). A mixture of 0.95 g. of III, 6 cc. of acetic acid, and 6 cc. of 6 *N* hydrochloric acid was refluxed five hours, cooled to 25°, diluted with 25 cc. of water, and extracted several times with ether. The aqueous layer was treated with Norit, filtered, and the filtrate was evaporated to dryness *in vacuo* at 50°. The crystalline residue was dissolved in ethanol, treated with Norit, filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue consisted of 0.25 g. of tan crystals of *2-methyl-3-amino-4-ketothiophane hydrochloride (IV).*

A solution of 200 mg. of IV in 3 cc. of water was treated with Norit and filtered. The resulting water-white solution was treated with 200 mg. of potassium cyanate. The latter dissolved readily and colorless crystals of V separated rapidly. After ten minutes the product was filtered and washed with 1 cc. of water; m.p. 172–175° (dec.); yield 55 mg. (16% from III).

Anal. Calc'd for $C_6H_8N_2OS$: C, 46.2; H, 5.1; N, 17.9; S, 20.5.
Found: C, 46.1; H, 5.7; N, 18.4; S, 20.5.

SUMMARY

A synthesis of *dl*-2-keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole is described, which involves Dieckmann cyclization of ethyl α-benzamido-β-carbethoxymethylthiobutyrate, acid hydrolysis of the keto ester so obtained, and treatment of the resultant 2-methyl-3-amino-4-ketothiophane hydrochloride with potassium cyanate.

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[Contribution from the Laboratorio de Química Orgánica, Facultad de Ciencias Exactas, Físicas y Naturales and Instituto de Fisiología, Facultad de Ciencias Médicas]

STUDIES ON ARGENTINE PLANTS. VIII. THE ALKALOIDS OF *ERYTHRINA CRISTA GALLI*. CHROMATOGRAPHIC SEPARATION OF ERYTHRATINE AND ERYSODINE

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Erythrina crista galli is the most common species of *Erythrina* in Argentina. Cicardo and Hug (1) found that, as with other *Erythrina* species, extracts of its seeds had curare-like activity, and Deulofeu, Hug, and Mazzocco (2) isolated hypaphorine from them. An examination of the seeds for alkaloids by Folkers, Shavel, and Koniuszy (3) showed the existence of free alkaloids that were not further identified, and of the liberated alkaloids erysodine and erysopine. Gentile and Labriola (4) isolated from them a mixture of crystalline hydriodides of the free alkaloids, and among the liberated ones erysovine as well as erysodine and erysopine.

New work on both fractions starting with larger quantities of seeds demonstrated the presence of erythramine, erythratine, and erythraline among the free alkaloids by separation as hydriodides, and of erythratine by isolation of the free base and preparation of some derivatives.

Erythraline seems to be the major alkaloid in the free state, followed by erythratine and erythramine.

The presence of erysopine, erysodine, and erysovine was confirmed in the liberated alkaloid fraction, erysopine being the major alkaloid and erysovine that present in the smallest amount. The hydrochlorides of erysopine and erysovine could be prepared and were found to be fairly stable in water solution.

We found that sometimes mixtures of erythratine and erysodine were produced that melted at 157–160° and were rather difficult to separate by crystalization. The alkaloids can be separated by chromatographic analysis; erysodine passed with the first fractions of solvent and erythratine with the last ones.

Hypaphorine was isolated in 1.25% yield.

EXPERIMENTAL

Erythratine. Seven kg. of *Erythrina crista galli* seeds were worked up according to the method described by Folkers and Koniuszy (5) as the preferred procedure. Eighteen and five-tenths grams (0.26%) of a syrup corresponding to the free alkaloid fraction was obtained. It was dissolved in 45 cc. of absolute ethanol and kept at 5°. A crystalline precipitate formed with time, and after some days it was filtered and recrystallized from ethanol. Eight hundred sixty milligrams of crystals melting at 171–172° was obtained, that was characterized as erythratine; $[\alpha]_D$ +138.6° (ethanol, $c = 0.39$).

Anal. Calc'd for $C_{18}H_{21}NO_4 + 0.5\ H_2O$: N, 4.32. Found: N, 4.67.

Erythratine hydriodide melted at 240°; $[\alpha]_D$ +110° (water, $c = 0.209$), and erythratine hydrobromide melted at 250°; $[\alpha]_D$ +149° (water, $c = 0.288$).

Erythratine hydrochloride. A small amount of erythratine suspended in absolute ethanol was dissolved by the addition of the required amount of hydrochloric acid. Ether was added to faint turbidity and the solution kept overnight at 5°. Crystals were obtained which were purified from ethanol, m.p. 250°, long prisms; $[\alpha]_D$ +165.1° (water, $c = 0.333$).

Anal. Calc'd for $C_{18}H_{21}NO_4 \cdot HCl$: C, 61.45; H, 5.97.
Found: C, 62.03; H, 6.03.

Folkers and Koniuszy (6) give for erythratine base hemihydrate m.p. 170–170.5°, $[\alpha]_D$ +144.9°; for the hydriodide, m.p. 242°, $[\alpha]_D$ +109°; and for the hydrobromide m.p. 241°, $[\alpha]_D$ +158.7°.

Erythraline hydriodide. The free alkaloid fraction corresponding to 5 kg. of seeds, from which erythratine base had been separated was treated in absolute ethanol solution with 6.11 g. of sodium iodide and 3.86 g. of acetic acid. One cubic centimeter of water was added, and by long standing at 5° a crystalline precipitate appeared, yield 1.98 g., m.p. 230°. Recrystallized four times from water, 1.1 g. of yellow needles was obtained, m.p. 252°, $[\alpha]_D$ +176° (water, $c = 0.229$).

Anal. Calc'd for $C_{18}H_{19}NO_3 \cdot HI$: N, 3.29. Found: N, 3.38.

Erythraline hydriodide melts at 252–253° and has $[\alpha]_D$ +177°.

Erythramine hydriodide. The mother liquors from the preparation of erythraline hydriodide were concentrated to one-half, and the crystals appearing after cooling collected. By another concentration, crystals were produced again, combined weight, 180 mg. They were recrystallized from water, the first crystals separated, and the mother liquor concentrated; 18 mg. of yellow needles melting at 242–243°, $[\alpha]_D$ +222.8° (water, $c = 0.166$). Erythramine hydriodide melts at 242° and has $[\alpha]_D$ +221°.

Hypaphorine and liberated alkaloids. The aqueous solution corresponding to 5 kg. of seeds, that had been extracted with chloroform for the free alkaloids, was acidified to Congo Red and kept a week at 5°. Sixty-two and five-tenths grams of crude hypaphorine hydrochloride was collected. The remaining solution was then boiled for 5 minutes, made alkaline with sodium bicarbonate, and extracted 20 times with 50 cc. of chloroform. The chloroform was evaporated, and from the residue after solution in alcohol and crystallization, 2.69 g. of crystals melting at 197° was isolated. Repetition of the hydrolysis for 30 minutes in acid medium (Congo Red) and extraction under the same conditions gave 7.5 g. of crystals melting at 198–200°.

A new acid hydrolysis was made lasting for one hour. When the solution was alkalified with sodium bicarbonate, a white precipitate was produced, which was filtered. Each time that chloroform was added, a precipitate formed; total 27 g. of the precipitated crystals, m.p. 230–235°. The chloroform extracts yielded 580 mg. of crystals melting at 198–200°.

A new acid hydrolysis of one hour gave only 3 g. of precipitate melting at 230–235° and no appreciable residue in the chloroform.

Erysodine. The 10.8 g. of crystals melting around 200° was combined and recrystallized from ethanol, using decolorizing charcoal the first time. Six and two-tenths grams of pure erysodine melting at 202–204° with $[\alpha]_D$ +250° in ethanol was obtained.

Erysopine. The 30 g. of precipitated crystals melting at 230–235° was purified by suspending in a large amount of ethanol, adding acetic acid to solution, boiling with charcoal, and after filtering, adding dilute ammonia to neutralization. Seventeen grams of erysopine melting at 240–241° was obtained. Recrystallization from ethanol gave a product melting at 242–243° and with $[\alpha]_D$ +261° (40% glycerol: 60% ethanol); intense green color with ferric chloride.

Erysopine hydrochloride. Two grams of erysopine was suspended in a small amount of water and concentrated hydrochloric acid added drop by drop. The erysopine dissolved, and on further addition, the hydrochloride crystallized out, yield 1.3 g. of prisms that can be recrystallized from water. It melted at 260–265° (slow heating) or 270° (rapid heating) with decomposition and previous darkening. The solution gave an intense green color reaction with ferric chloride; $[\alpha]_D$ +248° (water, $c = 0.327$); calculated on the basis of the erysopine content, $[\alpha]_D$ +279°. Folkers, Shavel, and Koniuszy (3) found $[\alpha]_D$ +276° for the same alkaloid dissolved in 0.5% hydrochloric acid.

Anal. Calc'd for $C_{17}H_{19}NO_3\cdot HCl$: C, 63.45; H, 6.22; N, 4.35.
Found: C, 63.10; H, 6.04; N, 4.83.

Erysovine. The ethanolic mother liquors from the purification of erysodine yielded on evaporation a crop of crystals melting at 163–165°. By chromatographic analysis as described by Folkers and Shavel (7), 370 mg. of crystals melting at 179° was obtained; $[\alpha]_D$ +239° (ethanol, c = 0.416).

Erysovine hydrochloride. Two grams of erysovine was suspended in 4 cc. of ethanol and concentrated hydrochloric acid (d, 1.19) added to solution. Ether was then added drop by drop, until crystals formed. More ether was added and, after 24 hours at 5°, the crystals were recrystallized from ethanol; obtained as needles melting at 237–238°. This hydrochloride retains water and had to be dried at 120° in a vacuum for 8 hours to obtain an analytical sample.

Anal. Calc'd for $C_{18}H_{21}NO_3\cdot HCl$: C, 64.28; H, 6.25.
Found: C, 64.12; H, 6.95.

$[\alpha]_D$ +233.8° (water, c = 0.686); calculated on the basis of the erysovine content, $[\alpha]_D$ +262°.

Erysovine in 0.5% hydrochloric acid has $[\alpha]_D$ +264.9° (c = 0.609).

Chromatographic analysis of mixtures of erythratine and erysodine. In some cases, when the chloroform extraction of the free alkaloids was done with some delay, it was found that after dissolving the residue from the chloroform extract in ethanol, crystals were obtained melting at 152–157°, that by recrystallization from the same solvent could not be purified to a higher melting point than 160°.

TABLE I

CHROMATOGRAPHIC SEPARATION OF ERYSODINE AND ERYTHRATINE

FRACTION	CHLOROFORM, CC	RESIDUE, MG.	M.P. °C.
I	70	124	200
II	50	559	157
III	50	234	172
IV	50	110	170
V	50	80	170

They were found to be a mixture of erythratine and erysodine that could be separated by chromatographic analysis on aluminum oxide with chloroform as solvent.

As an example, one fraction of 1.3 g. melting at 152–157° was dissolved without further purification in 100 cc. of chloroform and chromatographed through a column of aluminum oxide of 200 x 15 mm., and developed with chloroform. The fractions shown in Table I were collected.

Fractions I and II crystallized on evaporation. Fractions III–V gave a syrupy residue that was induced to crystallize by addition of ether. By recrystallization from ethanol, fraction I yielded pure erysodine melting at 202–204°; $[\alpha]_D$ +248° (ethanol).

Fractions III–V were united and recrystallized from ethanol, whereby pure erythratine base was obtained, melting at 172–173°; $[\alpha]_D$ +134.1° (ethanol). For further identification the hydriodide was prepared, m.p. 241°; $[\alpha]_D$ +111° (ethanol).

Fraction III was separated again into erysodine and erythratine by a new chromatograph.

SUMMARY

A reinvestigation of the seeds of *Erythrina crista galli* confirmed the presence of hypaphorine and of the liberated alkaloids erysodine, erysopine, and erysovine.

Erythratine, erythraline, and erythramine were characterized among the free alkaloids.

The hydrochlorides of the liberated alkaloids erysopine and erysovine are described.

Mixtures of erythratine and erysodine difficult to separate by crystallization can be separated by chromatographic analysis.

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THE SYNTHESIS OF *l*(−)-LEUCYLGLYCYLGLYCINE[1]

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The preparation of relatively large quantities of a number of peptides (2, 3) required for certain enzyme studies during the war period was undertaken in the writers' laboratory. The preparation of *l*(−)-leucylglycylglycine is described in the present report, since there are no entirely adequate literature methods for the synthesis of this tripeptide. The only recorded synthesis is that of Abderhalden and Fodor (4) who prepared 2.5 g. of the crude peptide by amination of *d*-α-bromoisocapronylglycylglycine. The latter compound was synthesized by the reaction of *d*-α-bromoisocapronyl chloride and glycine anhydride. The preparation of less than 1 g. of carbobenzoxy-*l*(−)-leucylglycylglycine by the hydrazide procedure has been described by Bergmann *et al.* (5).

EXPERIMENTAL

2,5-Diketopiperazine (glycine anhydride). This method is a modification of that described by Sannié (6). A mixture containing 700 g. of technical glycine and 3500 ml. of technical ethylene glycol is heated for 50 minutes at 174–176° with continuous stirring in a 5-l. round-bottom flask. The mixture is cooled for 20 hrs. in the refrigerator, the suspension is centrifuged and the brown crystalline precipitate is washed on a Büchner funnel with absolute methanol (1500 ml. total volume) until the washings are nearly colorless. The brown-colored 2,5-diketopiperazine (about 320 g.) is dissolved in 2.2 l. of boiling water and the solution is cooled overnight in the refrigerator The suspension is filtered and the light brown crystals are washed with absolute methanol (500 ml.) and dried in air. The product (about 250 g.) is dissolved in 2.5 l. of boiling water, the solution is decolorized with 20 g. of carbon (Nuchar XXX) and the suspension is filtered on a steam-heated Büchner funnel. If the filtrate is yellow, the decolorization procedure is repeated using 5 g. of carbon. The colorless filtrate is cooled overnight in the refrigerator, the suspension is filtered and the crystals are washed in turn with 100 ml. of ice-water, 80 ml. of 50% methanol and 80 ml. of absolute methanol. The yield is 210 g. (40%) of air-dried, pure white 2,5-diketopiperazine. An additional 22% of the product may be readily obtained from the filtrates but the approximately 14% remaining in the glycol residue is not conveniently recovered. The remaining 25% of the original glycine is converted to other products as indicated by the ammoniacal odor of the gases evolved and the black color of the reaction mixture.

Glycylglycine hydrochloride monohydrate. A mixture, prepared by adding 205 g. (1.8 moles) of diketopiperazine to 1100 ml. of hot C. P. concentrated HCl, is immediately heated to boiling, boiled for 90–100 seconds[2] and immediately cooled in an ice-water bath. After an hour the crystal mass is filtered on acid-resistant paper. The crystals are washed with three 90-ml. portions of 95% ethanol and dried at 50°. The yield of glycylglycine hydrochloride monohydrate is 300 g. (89%). The product may be purified by recrystallization from water and 95% ethanol.

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[1] Paper 38. For Paper 37, see Sexton and Dunn (1). Aided by grants from the Ella Sachs Plotz Foundation and the University of California. Preliminary studies were were carried out by E. A. Murphy. The authors are indebted to H. Block, W. Frankl, and H. Weil for technical assistance and to M. P. Stoddard for valuable suggestions.

[2] The first-order reaction rate constants for the hydrolysis in boiling concentrated HCl of diketopiperazine and glyclyglycine, were found to be about 0.05 and 0.0006, respectively, per second. The optimum single-heating time was calculated from these values to be 90 seconds. The yield is increased about 3% by reheating the filtrate as suggested by Fischer and Fourneau (7). The first heating should be limited to 30 seconds and the second (of the filtrate) to 90 seconds.

Anal. Calc'd for $C_4H_{11}ClN_2O_4$: N, 15.01; Eq. wt., 186.6.
Found: N, 14.84, 14.83; Eq. wt. by electrometric titration to *p*H 5.6, 185.2.

Glycylglycine ethyl ester hydrochloride.[3] The following procedure is based on the alternative method of Fischer and Fourneau (7). The preferred method (treatment of diketopiperazine with ethanol-HCl) of these workers was abandoned since only impure products difficult to purify were produced in several trials. A 3-l., three-necked, round-bottom flask is fitted with a reflux condenser, a motor stirrer, an outlet to a gas trap (8) and an inlet tube for dry HCl. One hundred sixty grams (0.86 mole) of glycylglycine hydrochloride monohydrate and 2400 ml. of absolute ethanol are placed in the flask, about 250 g. of dry hydrogen chloride from a tank or generator is introduced with stirring and cooling, and the mixture is boiled vigorously for just 10 minutes on the steam-bath. The steam-bath is immediately replaced by an ice-water bath and the mixture is stirred continuously for 2 hours. The suspension is filtered and the crystals are washed with 50 ml. of ice-cold absolute ethanol. The crude ester is recrystallized from 2400 ml. of absolute ethanol and the product is dried at 50°. An additional 140 g. (0.21 mole) of glycylglycine hydrochloride monohydrate is suspended in the ethanolic filtrate and the peptide is esterified and recrystallized as described. The total yield of recrystallized product is 250 g. (84%). The product contains less than 0.5% of free dipeptide as determined by titration with standard base using methyl red indicator. The melting point is 181–182°. Fischer and Fourneau (7) reported the melting point as 182°, with decomposition.

Glycylglycine ethyl ester (7). Eighty grams (0.41 mole) of glycylglycine ethyl ester hydrochloride is dissolved in a mixture of 56 ml. of water and 170 ml. of chloroform. The mixture is placed in a freezing bath and is cooled to −15°. A solution of 18 g. (0.45 mole) of NaOH in 44 ml. of water, cooled to −15°, is added slowly with constant stirring. One hundred grams of anhydrous K_2CO_3, cooled to −15°, is added and the mixture is thoroughly stirred until a clear supernatant layer of chloroform forms. The chloroform layer is decanted into a flask immersed in a solid carbon dioxide-ethanol bath. The residue is shaken with three 55-ml. portions of cold chloroform and the extracts are decanted into the flask. The combined chloroform extracts are kept cold in the carbon dioxide-ethanol bath until the carbobenzoxy-*l*(−)-leucine azide is ready for use.

l(−)*-Leucine methyl ester hydrochloride.* Dry hydrogen chloride (about 100 g.) is passed for 2 hours with continuous stirring into a mixture containing 250 *g*. of purified *l*(−)-leucine (9) suspended in 1500 ml. of absolute methanol. The solution is distilled under reduced pressure and the residual thick mass of crystals is cooled to 0° and filtered. A second crop of crystals is obtained by treating the filtrate similarly. Both crops of crystals are dried *in vacuo* over NaOH. The first crop is recrystallized once from 6 parts of 1:5 methanol-diisopropyl ether. The second crop is recrystallized once from the mother liquor of the first crop, and once from 6 parts of 1:5 methanol-diisopropyl ether. The total yield of *l*(−)-leucine methyl ester hydrochloride is 260 g. (75%). The product melts at 147–148° and contains about 2% of *l*(−)-leucine hydrochloride as determined by titration with standard base using methyl red indicator. The twice recrystallized product is free of *l*(−)-leucine hydrochloride and melts at 150–151°. Smith and Brown (10) reported the melting point 149–150° for *d*(+)-leucine methyl ester hydrochloride.

Anal. Calc'd for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.88; N, 7.71; Cl, 19.52.
Found: C, 47.07; H, 8.97; N, 7.7; Cl, 19.64.
$[\alpha]_D^{25.9}$ −13.40° (water, *c* = 5.0775).

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[3] The analogous isopropyl ester was prepared by the described procedure except that 2-propanol was substituted for ethanol and the mixture was heated for 60, instead of 10 minutes. The product, m.p. 199–202°, was nearly pure as indicated by titration with standard base and the indicators, alizarine sulfonate and thymolphthalein.

Carbobenzoxy-l(−)-leucine methyl ester (11). Twelve hundred milliliters of chloroform and a solution containing 260 g. (1.43 moles) of *l*(−)-leucine methyl ester hydrochloride dissolved in 650 ml. of water are placed in a 3-l. beaker immersed in an ice-water bath. The electrodes of a *p*H meter, a motor stirrer, and a thermometer are placed in the solution. Two dropping-funnels, one containing 228 ml. (270 g. or 1.4 moles) of a 90% solution of carbobenzoxy chloride (benzyl chloroformate[4]) and the other 250 ml. of 6 *N* NaOH, are clamped so that their outlets extend nearly to the surface of the solution. The solution is stirred and, when the temperature falls to 15°, saturated NaOH (about 79 ml. or 1.43 moles) is added dropwise until the *p*H rises to about 10.0. The carbobenzoxy chloride and 6 *N* NaOH (about 238 ml. or 1.43 moles) are added simultaneously and at such a rate that the *p*H is maintained between 10.0 and 10.5. The temperature is kept between 25° and 35° during the addition (about 60 minutes) of these reagents. When all of the carbobenzoxy chloride has been added the addition of 6 *N* NaOH is discontinued and stirring is continued for 45 minutes. Ten milliliters of pyridine is added[5] and the mixture is acidified to *p*H 2.0 with 6 *N* HCl (about 79 ml. or 1.43 moles). The mixture is transferred to a 3-l. separatory funnel. The chloroform layer is separated and is extracted twice with 600-ml. portions of water, twice with 400-ml. portions of *N* $NaHCO_3$, once with 400 ml. of *N* HCl and once with 600 ml. of water.

The washed chloroform solution is clarified by shaking it with anhydrous Na_2SO_4, the chloroform is removed by distilling the filtrate under reduced pressure and the resulting syrup is purified by adding 100 ml. of water and distilling the solution under reduced pressure. Further purification is effected by adding 50 ml. of ethanol and distilling the solution under reduced pressure. The product is placed for 24 hours in a vacuum desiccator over concentrated sulfuric acid to remove most of the benzyl chloride.[5] The light brown syrupy carbobenzoxy-*l*(−)-leucine methyl ester can be used without further purification for the preparation of the hydrazide. The yield of product is 380 g. (95%).

Carbobenzoxy-l(−)-leucine hydrazide (11). One hundred fifteen milliliters (2.0 moles) of 85% hydrazine hydrate is added to 380 g. (1.37 moles) of syrupy carbobenzoxy-*l*-(−)-leucine methyl ester. The mixture is allowed to stand for 48 hours at room temperature with occasional shaking. During this time the two-phase liquid system gradually becomes homogeneous and eventually solidifies with the evolution of heat. The white cake of hydrazide is dissolved in 800 ml. of hot ethyl acetate. The solution is filtered and placed overnight in the refrigerator. The suspension is filtered and the crystals are washed with a total of about 2 l. of a 3:8 mixture of peroxide-free diethyl ether and petroleum ether. The product is recrystallized from 2.3 ml. of hot ethyl acetate per gram of crude hydrazide. The yield of carbobenzoxy-*l*(−)-leucine hydrazide, m.p. 118–120°, is 250 g. (68%). An additional 75 g. (20%) may be obtained by combining the filtrates and washings, concentrating the solution to a syrup *in vacuo*, adding 35 ml. of hydrazine hydrate, and treating as described. Further purification may be effected by recrystallizing the crude product from ethyl acetate, hot water, 20% ethanol in water or 20% ethanol in petroleum ether or by dissolving it in HCl and precipitating it with $NaHCO_3$. The melting point of the purified product is 120–122°. Bergmann *et al.* (11) found 121° while Smith and Brown (10) reported that carbobenzoxy-*d*(+)-leucine hydrazide melted at 121°. $[\alpha]_D^{25.2}$ −21.31° (95% ethanol, $c = 4.994$).

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[4] Carter *et al.* (12) have described methods for preparing and determining the strength of carbobenzoxy chloride. An excess of this reagent should be avoided since it introduces objectionable impurities.

[5] If an excess of carbobenzoxy chloride is present, the *p*H of the solution may fall one to two units owing to the formation of carbon dioxide (13) and benzyl chloride from carbobenzoxy chloride by the catalytic action of the pyridine. Benzyl chloride dissolves in the chloroform layer and is responsible for the acrid odor of the final product. Benzyl chloride reacts with hydrazine and tends to contaminate the hydrazide.

Carbobenzoxy-l-(—)-leucine azide (12). A solution of 80 g. (0.29 mole) of carbobenzoxy-*l*(—)-leucine hydrazide in a mixture containing 200 ml. of glacial acetic acid, 100 ml. of concentrated HCl, and 500 ml. of water is placed in a 2-l. round-bottom flask fitted with a mechanical stirrer. The flask is set in a freezing bath and, when the temperature is about —12°, a cold solution of 21.5 g. (0.31 mole) of $NaNO_2$ in 107 ml. of water is added. A yellowish oil forms immediately and rises to the surface. The oily layer is taken up in 600 ml. of cold (—15°) ether and the mixture is poured rapidly into a separatory funnel which has been thoroughly chilled by flushing it with ice-water. The aqueous phase is drawn off as quickly as possible and about 3 l. of ether-saturated ice-water is run through the ether solution (without shaking) as rapidly as possible. The ether solution of the carbobenzoxy-*l*(—)-leucine azide is transferred immediately to a 1-liter flask set in a carbon dioxide-ethanol bath.

Carbobenzoxy-l(—)-leucylglycylglycine ethyl ester (5).[6] A 2-l. Florence flask is fitted with a two-hole cork carrying a thermometer and an outlet to a gas trap (8) to absorb the highly toxic hydrazoic acid. The previously described cold chloroform solution of the glycylglycine ethyl ester and the ether solution of the carbobenzoxy-*l*(—)-leucine azide are transferred in turn to the flask. If necessary to facilitate pouring, these solutions may be thawed in an ice-salt bath. The reaction mixture is heated for 7 hours at about 45°. The chloroform-ether solution, cooled to room temperature, is washed successively with three 250-ml. portions of *N* $NaHCO_3$, one of water, three of *N* HCl, and one of water. The washed solution is dried over Na_2SO_4 and evaporated to a syrup under reduced pressure. Two 30-ml. portions of ether are added and then removed by distillation *in vacuo*. Fifteen hundred milliliters of ether is added and the residue is dissolved by warming the mixture. The solution is filtered if necessary to remove undissolved material, the filtrate is stirred at intervals until crystals form, and the mixture is placed overnight in the refrigerator. The suspension is filtered, the precipitate is suspended in 700 ml. of ether, and the mixture is refluxed for 30 minutes, filtered, and dried at 50°. This product should be redigested with ether if its melting point is below 103°. The yield usually is about 60 g. (50%) based on the carbobenzoxy-*l*(—)-leucine hydrazide. Occasionally lower yields are encountered. Among the side reaction products, an ether-soluble solid melting at 123° and an acidic oil, soluble in *N* $NaHCO_3$ were isolated. The crude product, recrystallized from 50% ethanol, melts at 103–104.5°. Bergmann *et al.* (5) reported 105°. $[\alpha]_D^{25.1}$ —10.98° (95% ethanol, *c* = 5.010).

Carbobenzoxy-l(—)-leucylglycylglycine (5).[7] A solution of 61 g. (0.16 mole) of carbobenzoxy-*l*(−)-leucylglycylglycine ethyl ester in 600 ml. of methanol is filtered into a 4-l. beaker. Ninety milliliters of 2 *N* NaOH is added with stirring. After the solution has stood for 15 minutes, sufficient (about 33 ml.) 6 *N* HCl is added to give a red color with methyl orange paper. One liter of ethyl acetate is added with stirring followed by 1200 ml. of distilled water. The phases are separated with a 4-l. separatory funnel, the aqueous layer is extracted four times with 200-ml. portions of ethyl acetate and discarded, and the five ethyl acetate solutions are combined and shaken in a 4-l. flask with 450 ml. of *N* $NaHCO_3$. The phases are separated, the ethyl acetate layer is extracted three times with 150-ml. portions of *N* $NaHCO_3$ and the ethyl acetate is discarded. The four aqueous extracts are transferred to a 3-l. beaker and immediately acidified with 140 ml. of 12 *N* HCl. The thick oil which separates from the solution is taken up in 250 ml. of ethyl acetate and the water layer is extracted twice with 250-ml. portions of ethyl acetate and discarded. The combined ethyl acetate extracts are dried with anhydrous sodium or magnesium sulfate, decanted or filtered into a 2-l. round-bottom flask and evaporated to a syrup under reduced pressure. Two 30-ml. portions of anhydrous ethyl acetate are added and removed by distillation under reduced pressure. The residue is brought into solution by adding 300 ml. of anhydrous ethyl acetate and warming the mixture. (Occasionally, the product crystallizes as the solvent is being removed and about 1300 ml. of ethyl acetate is required to redissolve it.) Crystallization is induced by scratching the inner surface of the flask with a glass rod at intervals for several hours. When copious crystallization has occurred the flask is placed in the refrigerator for 24 hours. The suspension is filtered, the crystals are washed with 25-ml. of ether and dried at 50°, and the filtrate is placed overnight in the refrigerator. The flask is scratched occasionally to ensure complete crystallization. The yield of crude product, m.p. 133–140°, is 35 g. (62%). The crude product is recrystallized from 2 l. of ethyl acetate. The yield of purified carbobenzoxy-*l*-(−)-leucylglycylglycine, m.p. 144–145°, is 30 g. (85 % recovery). Bergmann *et al.* (5) reported 144° as the melting point and $[\alpha]_D^{22}$ −12.8° (alcohol, $c = 4.9$).

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[6] The analogous isopropyl ester was prepared by a similar procedure. The product, m.p. 88–89°, was more difficult to crystallize and purify than the corresponding ethyl ester because of its greater solubility in ether and other solvents.

[7] The tendency of ethyl acetate solutions to spill down the sides of a beaker when poured is counteracted by lubricating the glass under the pouring lip with silicon lubricant (Dow-Corning stop-cock grease).

The relation of yield to hydrolysis time has not been critically studied although prolonged treatment with alkali was avoided to minimize hydrolysis and racemization of the peptide. Even under the mild conditions employed, there was recovered from the combined filtrates from the crystallization of 160 g. of carbobenzoxy-*l*(—)-leucylglycylglycine, 9 g. of a white crystalline substance (m.p. 165–168°) believed to be *dl*-5-isobutylhydantoin-3-acetylglycine as indicated by the following analytical data. The compound had no appreciable specific rotation (—0.03°) in 95% ethanol.

Anal. Calc'd for $C_{11}H_{17}N_3O_5$: C, 48.70; H, 6.32; Eq. wt., 271.3.

Found: C, 49.76; H, 6.43; Eq. wt. by electrometric titration, 267.

The highly acidic character of the compound is indicated by its *p*K value (3.90 in 29% ethanol).

The formation of hydantoins from carbethoxy peptides (14) and the racemization of hydantoins in dilute alkali (15) have been studied by the authors cited.

Anal. Calc'd for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08; Eq. wt., 379.4.
Found: C, 57.89; H, 6.74; N, 10.59, 10.60; Eq. wt. by electrometric titration, 376.4.
$[\alpha]_D^{25}$ −14.28° (95% ethanol, $c = 4.955$).

l(−)-*Leucylglycylglycine.* To a solution of 88 g. (0.23 mole) of carbobenzoxy-*l*(−)-leucylglycylglycine in 880 ml. of methanol in a 2-l. flask are added 0.4 g. of activated palladium oxide (16) and 44 ml. of glacial acetic acid. The flask is fitted with inlet and outlet tubes and is shaken in a mechanical shaker while hydrogen is bubbled through the solution at room temperature and pressure. The hydrogenation is continued (1 to 6 days) until no more carbon dioxide is evolved (determined by passing the gas through barium hydroxide solution in a trap) upon the addition of 0.05-g. portions of fresh catalyst. The precipitated tripeptide is dissolved by adding 175 ml. of water and heating the mixture on a steam-bath. The suspension of catalyst is filtered, washed with 80% ethanol and preserved for reactivation. The combined clear filtrate and washings are distilled under reduced pressure and the residual crude *l*(−)-leucylglycylglycine is dissolved by adding 120 ml. of water and heating the mixture on a steam-bath. The solution is cooled to room temperature, 80 ml. of absolute 2-propanol is added and the solution is filtered. Five hundred sixty milliliters of 2-propanol is added to the filtrate and the mixture is heated over a steam-bath until crystals form. The mixture is placed for 24 hours in the refrigerator. The suspension of crystals is filtered and the precipitate is dried *in vacuo*. The yield of crude product is 56 g. (98%). The crude product is recrystallized by dissolving it in 125 ml. of water and adding 670 ml. of 2-propanol to the solution. The yield of purified *l*(−)-leucylglycylglycine, obtained as bulky, finely crystalline powder, is 50 g. (89% recovery).

The tripeptide is nearly insoluble in cold 88% 2-propanol, slightly soluble in methanol, and soluble in 1.6 parts of boiling water, and 2.5 parts of water at 5°. The following approximate solubilities at 5° (given in the parentheses in g. per 100 g. of solvent) were found at the indicated percentage concentrations of 2-propanol in water: 0 (39.2), 66 (5.8), 78 (0.6), 84

(0.15), and 88 (0.0). Precipitation of the tripeptide from 90 and higher percentage concentrations of 2-propanol is incomplete in 20 hours and the precipitates are extremely fine and difficult to filter. Purification is more satisfactory with an 81% solution of 2-propanol. The tripeptide liquefies in 30 seconds when it is placed in an open Pyrex capillary tube and the latter is plunged into a bath at 220° (uncorr.). The apparent specific volume of 0.728 ml./g. was calculated from the densities of 0.206 molar solution at 15°, 20°, 25°, and 30°. The apparent molal volume, 178 ml., is the same as that found by Greenstein and Wyman (17) for *dl*-leucylglycylglycine in 0.04 to 0.08 molal solutions. Specific rotations determined in a 4 dm. tube at temperatures (t) from 20° to 30° from concentrations (c) of 1.27 to 5.11 % are summarized in the following equation:

$$[\alpha]_D^{t^\circ} = +65.30^\circ - 0.46\,c + 0.017\,c^2 - 0.35\,t + 0.0046\,t^2.$$

The values reported by Abderhalden and Fodor (4) are 12° to 15° lower than those found for our product due, probably, to partial racemization during amination. The probable high purity of our tripeptide preparation was established by the further observation that the specific rotations of 5.000% solutions at 25° were + 57.56° for the original purified product (A), +57.72° for the product (B) obtained by recrystallization of (A) from water, and +57.56° for the product obtained by precipitating it with alcohol from the filtrate of (B).

Anal. Calc'd for $C_{10}H_{19}N_3O_4$: N, 17.13. Found: N, 17.18, 17.22.

SUMMARY

Methods have been described for the synthesis of 50 g. of purified $l(-)$-leucylglycylglycine by the following reactions: Glycine → glycine anhydride → glycylglycine hydrochloride monohydrate → glycylglycine ethyl ester hydrochloride → glycylglycine ethyl ester. $l(-)$-Leucine → $l(-)$-leucine methyl ester hydrochloride → carbobenzoxy-$l(-)$-leucine methyl ester → carbobenzoxy-$l(-)$-leucine hydrazide → carbobenzoxy-$l(-)$-leucine azide. Glycylglycine ethyl ester + carbobenzoxy-$l(-)$-leucine azide → carbobenzoxy-$l(-)$-leucylglycylglycine ethyl ester → carbobenzoxy-$l(-)$-leucylglycylglycine → $l(-)$-leucylglycylglycine.

LOS ANGELES, CALIF.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

SOME 4-DIETHYLAMINO-1-METHYLBUTYLAMINOPYRIMIDINES[1]

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AND ROBERT H. REITSEMA

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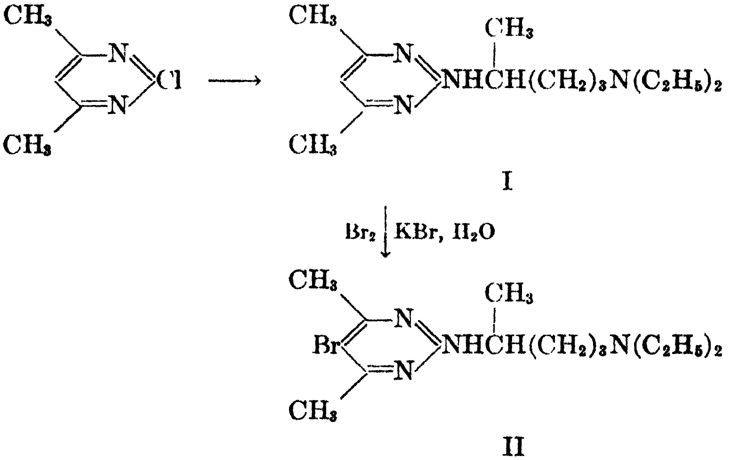
In view of the antimalarial activity of a number of quinoline and quinazoline derivatives bearing dialkylaminoalkylamino side chains, it seemed of some interest to prepare a few simple analogs in the pyridine and pyrimidine series. This paper reports the preparation of four compounds in the latter class, none of which showed promise as antimalarial drugs.

2-Chloro-4,6-dimethylpyrimidine (I) coupled readily with 4-amino-1-diethylaminopentane. The product was brominated by treatment with aqueous bromine-potassium bromide to introduce a bromine in the 5-position (II, SN-14,303)[3].



I

II

An analog of I containing a methoxyl group on one of the ring methyl groups (SN-12,281) was prepared by coupling 4-amino-1-diethylaminopentane with 2-chloro-4-methyl-6-methoxymethylpyrimidine (2).

The pyrimidine portion of thiamin was coupled with 4-amino-1-diethylaminopentane to give a 2-methyl-4-amino-5-(4-diethylamino-1-methylbutylaminomethyl)pyrimidine (III, SN-13,261).

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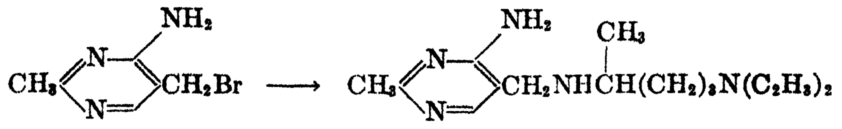
[1] The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

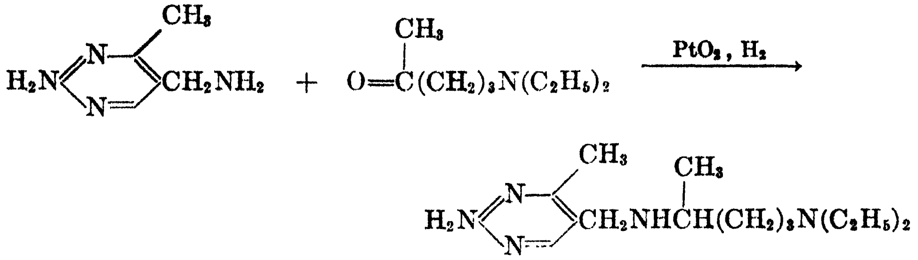
[2] Present address: University of Notre Dame, Notre Dame, Indiana.

[3] The Survey Number, designated SN-, refers to the number assigned a drug by the Survey of Antimalarial Drugs. The activities of these compounds are reported in the monograph "Antimalarial Drugs, 1941–1945," F. Y. Wiseolgle, Editor, Edwards, Ann Arbor, 1946.



III

An isomer (IV, SN-12,283) with the nuclear methyl and amino groups interchanged was prepared by reductive alkylation of 2-amino-5-aminomethyl-4-methylpyrimidine (3) with γ-diethylaminopropyl methyl ketone.



IV

EXPERIMENTAL[4]

2-(4-Diethylamino-1-methylbutylamino)-4,6-dimethylpyrimidine. 2-Chloro-4,6-dimethylpyrimidine (34 g., 0.24 mole), prepared by the method of St. Angerstein (1), and 76 g. (0.48 mole) of 4-amino-1-diethylaminopentane were heated on a steam-cone for thirteen hours. The residue was dissolved in ether, extracted with aqueous alkali, and dried over magnesium sulfate. Excess 4-amino-1-diethylaminopentane was then removed by heating the oil on a water-bath under reduced pressure (6 mm.). Sixty-three grams (89%) of crude amine was obtained, the bulk of which was subjected to bromination without further purification.

A sample of the *picrate*, m.p. 163–164.5°, was crystallized from ethanol.

Anal. Calc'd for $C_{15}H_{28}N_4 \cdot 2C_6H_3N_3O_7$: C, 44.88; H, 4.74

Found: C, 44.97; H, 4.69.

The *picrylsulfonate* was prepared by dissolving the amine in an equivalent amount of dilute aqueous hydrochloric acid and adding a solution of sodium picrylsulfonate. The derivative, after repeated recrystallization from ethanol, melted at 171–173°.

Anal. Calc'd for $C_{15}H_{28}N_4 \cdot 2C_6H_3N_3O_9S$: C, 38.12; H, 4.03.

Found: C, 38.09; H, 4.24.

5-Bromo-2-(4-diethylamino-1-methylbutylamino)-4,6-dimethylpyrimidine. The 2-(4-diethylamino-1-methylbutylamino)-4,6-dimethylpyrimidine (38 g., 0.14 mole) prepared above was dissolved in 20 cc. of concentrated hydrochloric acid and 100 cc. of water. A solution of 11 cc. (32 g., 0.20 mole) of bromine in 30 g. of potassium bromide and 250 cc. of water was then added. An oil separated which did not dissolve completely even after the addition of more hydrochloric acid. The suspension was shaken and allowed to stand for thirty minutes at room temperature. It was then added to 500 cc. of 20% sodium hydroxide and more solid sodium hydroxide was added until the solution was strongly basic. It was extracted with four 100-cc. portions of ether, the ether layer was dried over 50 g. of Drierite and the ether was removed by distillation. The dark oily residue was distilled twice under reduced pressure and 19.5 g. (41%) of yellowish oil, b.p. 139–142° (0.3 mm.), n_D^{20} 1.5368, was obtained. The compound was purified for analysis by redistillation; b.p. 145° (0.5 mm.), n_D^{20} 1.5362.

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[4] Analyses were performed by Miss Theta Spoor and Miss Lillian Hruda.

Anal. Calc'd for $C_{15}H_{27}BrN_4$: C, 52.35; H, 7.93; N, 16.32.
Found: C, 52.58; H, 8.07; N, 16.83.

The *picrate* was prepared in hot ethanol, in which it was very difficultly soluble, and recrystallized from a Methyl Cellosolve-ethanol mixture. It melted at 170–172°.

Anal. Calc'd for $C_{15}H_{27}BrN_4 \cdot 2C_6H_3N_3O_7$: C, 40.46; H, 4.15.
Found: C, 40.60; H, 4.29.

2-(4-Diethylamino-1-methylbutylamino)-4-methyl-6-methoxymethylpyrimidine. 2-Chloro-4-methyl-6-methoxymethylpyrimidine (2) (15.2 g., 0.088 mole, n_D^{20} 1.5120) and 28 g. (0.18 mole) of 4-amino-1-diethylaminopentane, which had been purified through the dithiocarbamate (4), were heated on a steam-cone for ten hours. The dark solution resulting was dissolved in ether, extracted with aqueous alkali, dried, and distilled. The product weighed 18.1 g. (70%), b.p. 127–128° (0.1 mm.), n_D^{20} 1.5066. It was redistilled for analysis; b.p. 128° (0.15 mm.), n_D^{20} 1.5063.

Anal. Calc'd for $C_{16}H_{30}N_4O$. C, 65.27; H, 10.27; N, 19.03.
Found: C, 65.03; H, 10.51; N, 19.80.

The *picrate*, prepared in and recrystallized from ethanol, melted at 127–129°.

Anal. Calc'd for $C_{16}H_{30}N_4O \cdot 2C_6H_3N_3O_7$: C, 44.68; H, 4.82.
Found: C, 44.66; H, 4.93.

2-Methyl-4-amino-5-(4-diethylamino-1-methylbutylaminomethyl)pyrimidine. A solution of 43.6 g. (0.09 mole) of 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide, supplied by Merck and Company through the courtesy of Dr. Karl Folkers, and 52.8 g. (0.33 mole) of purified 4-amino-1-diethylaminopentane in 200 cc. of isopropyl alcohol was heated to 95° for eight hours. The alcohol was removed by distillation at atmospheric pressure. To the residue was added 100 cc. of benzene and this solution was extracted with 10 cc. of 3 *N* sodium hydroxide. Upon distillation of the benzene solution, two fractions were collected, 11 g. of material boiling at 138–200° (2 mm.) and 15.1 g. boiling at 245–250° (2 mm.). The latter fraction was not further investigated.

Upon redistillation of the lower-boiling fraction, the *first fraction* collected was 5.5 g. of yellow oil, boiling at 139–142° (2 mm.). The identity of this material was not obvious from analytical data.

Anal. Calc'd for $C_{14}H_{25}N_5O$: C, 60.18; H, 9.02; N, 25.07.
Found: C, 60.43, 60.55; H, 8.94, 8.88; N, 25.00, 24.71.

The *picrate*, prepared in ethanol, melted to a clear red liquid at 196–198°.

Anal. Calc'd for $C_{14}H_{25}N_5O \cdot 2C_6H_3N_3O_7$ C, 42.34; H, 4.24; N, 20.89.
Calc'd for $C_{11}H_{20}N_4 \cdot 2C_6H_3N_3O_7$: C, 41.46; H, 3.93; N, 21.02.
Found: C, 41.11, 41.36; H, 3.69, 3.93; N, 21.04, 21.17.

A *second fraction* (4.5 g.), boiling at 195–200° (2 mm.), n_D^{20} 1.5159, was the desired *2-methyl-4-amino-5-(4-diethylamino-1-methylbutylaminomethyl)pyrimidine.*

Anal. Calc'd for $C_{15}H_{29}N_5$: C, 64.47; H, 10.46; N, 25.07.
Found: C, 64.32; H, 10.54; N, 24.89.

The *picrate* did not crystallize.

2-Amino-4-methyl-5-(4-diethylamino-1-methylbutylaminomethyl)pyrimidine. Fifteen grams (0.11 mole) of 2-amino-4-methyl-5-aminomethylpyrimidine (3), 17.25 g. (0.11 mole) of γ-diethylaminopropyl methyl ketone, 0.15 g. of platinum oxide, and 120 cc. of absolute ethanol were mixed and heated in a bomb at 75° under an average pressure of 500 to 600 pounds of hydrogen. About twelve hours were required for the completion of the reduction. Four days were required for the reduction when carried out at room temperature and at a pressure of 2 to 3 atmospheres of hydrogen. The catalyst was removed, and to the filtrate was added 80 cc. of benzene. The solution was distilled at atmospheric pressure to remove ethanol, benzene, and water. The pressure was reduced to 18 mm. and a small amount of liquid distilled at 85°, which was presumably γ-diethylaminopropyl methyl carbinol.

The residue in the flask contained some unchanged aminomethylpyrimidine which could be recovered by distilling the mixture at 2 to 3 mm. pressure. At 170–180° a distillate was obtained which readily solidified in the receiver. It weighed 4.8 g., m.p. 145–154°. It did not depress the melting point of 2-amino-4-methyl-5-aminomethylpyrimidine. The picrate, m.p. 220–226° (dec.), similarly did not lower the melting point of a picrate of the starting material.

The remainder of the material in the flask was dissolved in petroleum ether (b.p. 90–100°), filtered from a small amount of the original pyrimidine, treated with Darco, and filtered. In this manner 10.6 g. (35%) of crude product was isolated. In another experiment, the distillation was omitted and the residue, after removal of carbinol, was freed from unchanged pyrimidine by recrystallization. After several recrystallizations from petroleum ether (b.p. 40–60° and 90–110°) and from benzene, the white, waxy plates of 2-amino-4-methyl-5-(4-diethylamino-1-methylbutylaminomethyl)pyrimidine melted at 89–90°.

Anal. Calc'd for $C_{15}H_{29}N_5$: C, 64.67; H, 10.46; N, 25.07.
Found: C, 64.42; H, 10.37; N, 25.12.

The *picrate*, prepared in ethanol, was an oil which turned solid after standing a day. The crude picrate melted at 150–166° (dec.), and attempts to recrystallize it were not successful. The *picrolonate* melted at 193–194° (dec.) after one recrystallization from ethanol and one from benzene.

SUMMARY

Five new dialkylaminoalkylaminopyrimidines have been prepared and characterized.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

SYNTHESIS OF PAREDRINE AND RELATED COMPOUNDS[1]

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Syntheses involving the nitro alkanes may provide attractive methods for preparing amines and amino alcohols. Since nitro alkanes have now become cheap and plentiful, these methods are of particular interest for the preparation of Paredrine, Propadrine, ephedrine, and other products which possess physiological action.

Paredrine, a proprietary name for *p*-hydroxyphenyl-2-propylamine, is a synthetically-prepared, racemic mixture of the $HO—C_6H_4—CH_2CHNH_2CH_3$ bases, which is marketed as the hydrobromide. Solutions are used for shrinking the nasal mucosa in head-colds and hay fever, for sinus irrigation, and in ophthalmology as an adjuvant to 1% atropine or 4% homatropine. It has the advantage of producing practically no stimulation of the central nervous system and a minimum of side effects.

Paredrine has now been made by two series of reactions, each involving nitroethane as an intermediate.

SYNTHESIS NUMBER ONE

In the first of these, *p*-nitrobenzyl chloride is condensed with a salt of nitroethane and the dinitro compound which results is reduced to a diamine. That amino group, which is attached to the benzene ring, is then replaced by a hydroxyl group by formation and decomposition of the diazonium salt.

$$\text{(I)}\quad p\text{-}O_2N—C_6H_4—CH_2Cl + NaO_2N{:}CHCH_3 \rightarrow p\text{-}O_2N—C_6H_4—CH_2—CHNO_2CH_3$$

$$\text{(II)}\quad p\text{-}O_2N—C_6H_4—CH_2CHNO_2 \xrightarrow[\text{Raney Ni}]{H_2\text{ and}} p\text{-}H_2N—C_6H_4—CH_2CHNH_2CH_3$$

$$\text{(III)}\quad p\text{-}H_2N—C_6H_4—CH_2CHNH_2CH_3 \xrightarrow[\text{then hydrolysis}]{NaNO_2\text{ and }HCl} p\text{-}HO—C_6H_4—CH_2CH(NH_2\cdot HCl)CH_3$$

SYNTHESIS NUMBER TWO

In this process *p*-methoxybenzaldehyde (anisaldehyde) is caused to react with nitroethane in an aldol-type condensation. The nitro alcohol which results loses water spontaneously, producing the nitro olefin. The nitro olefin is treated with iron and hydrochloric acid. In the course of the reduction, however, the desired oxime is hydrolyzed and the ketone, instead of the oxime, is isolated at the end of the reaction. It is therefore necessary to re-form the oxime by treating the ketone with hydroxylamine hydrochloride. The oxime is subsequently reduced, and the ether group attached to the ring is split with hydrochloric acid to yield a hydroxyl group.

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[1] A portion of the doctoral thesis of Fred W. Hoover.

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$$\text{(I)}\quad \begin{aligned} &p\text{-}CH_3O{-}C_6H_4CHO + CH_3CH_2NO_2 \rightarrow \\ &\qquad p\text{-}CH_3O{-}C_6H_4{-}CHOHCHNO_2CH_3 \rightarrow \text{unstable in acids} \\ &\qquad\qquad p\text{-}CH_3O{-}C_6H_4{-}CH{:}CNO_2CH_3 \end{aligned}$$

$$\text{(II)}\quad \begin{aligned} &p\text{-}CH_3O{-}C_6H_4{-}CH{:}CNO_2CH_3 \xrightarrow{Fe\ +\ HCl} \\ &\qquad p\text{-}CH_3O{-}C_6H_4CH_2{-}CO{-}CH_3 \end{aligned}$$

$$\text{(III)}\quad \begin{aligned} &p\text{-}CH_3O{-}C_6H_4{-}CH_2CO{-}CH_3 \xrightarrow{H_2NOH} \\ &\qquad p\text{-}CH_3O{-}C_6H_4{-}CH_2C({:}NOH)CH_3 \end{aligned}$$

$$\text{(IV)}\quad \begin{aligned} &p\text{-}CH_3O{-}C_6H_4{-}CH_2C({:}NOH)CH_3 \xrightarrow{H_2\ +\ Ni} \\ &\qquad p\text{-}CH_3O{-}C_6H_4CH_2CHNH_2CH_3 \end{aligned}$$

$$\text{(V)}\quad \begin{aligned} &p\text{-}CH_3O{-}C_6H_4{-}CH_2CHNH_2CH_3 + HCl \longrightarrow \\ &\qquad p\text{-}HO{-}C_6H_4CH_2CH(N_2H\cdot HCl)CH_3 \end{aligned}$$

DISCUSSION

Synthesis Number One

The synthesis beginning with *p*-nitrobenzyl chloride involves, at the outset, an aralkylation of a salt of an aci-nitro alkane. Although the aralkylation has not been studied extensively enough to permit of prediction in all cases, Weisler (5) has shown that it is correlated with the stability of the aci- form of the nitro compound, and is probably dependent on the rate at which the aci- form tautomerizes to the normal form. If the stability of the aci- form is high, the tendency is toward aralkylation on the carbon atom instead of on oxygen. Also, the greater the reactivity of the halide selected, as evidenced by its tendency to ionize or to form free radicals, the greater is the tendency for reaction with the carbon atom.

In the reaction between the salt of aci-nitroethane and *p*-nitrobenzyl chloride, aralkylation occurs both on carbon and on oxygen, but fortunately aralkylation on carbon greatly predominates. (Reaction with an oxygen produces minor quantities of a nitronic ester or its decomposition products; *p*-nitrobenzaldehyde was therefore isolated as a by-product in step one.) Another competing reaction, which takes place to a greater extent than reaction on an oxygen atom, is the formation of 1,1-bis-(*p*-nitrobenzyl)nitroethane. If no excess nitroethane is used, this reaction predominates over the reaction desired, but formation of the monoaralkylated product can be favored by using an excess of nitroethane so that disubstitution is largely suppressed. This effect can be explained by considering the following reactions:

$$\text{(I)}\ p\text{-}O_2N\text{—}C_6H_4CH_2Cl + O_2^-N{:}CHCH_3 \rightarrow p\text{-}O_2N\text{—}C_6H_4CH_2CH(NO_2)CH_3 + Cl^-$$

$$\text{(II)}\ p\text{-}O_2N\text{—}C_6H_4CH_2CH(NO_2)CH_3 + ON{:}C_2^-HCH_3 \rightleftarrows p\text{-}O_2N\text{—}C_6H_4CH_2C({:}NO_2^-)CH_3 + CH_3CH_2NO_2$$

$$\text{(III)}\ p\text{-}O_2N\text{—}C_6H_4CH_2Cl + p\text{-}O_2N\text{—}C_6H_4CH_2C({:}NO_2^-)CH_3 \rightarrow (p\text{-}O_2NC_6H_4CH_2)_2CNO_2CH_3 + Cl^-$$

Since the formation of the aralkylated product probably occurs in accordance with equation (III), the rate of its formation depends on the concentration of the ion, p-O_2N—$C_6H_4CH_2C({:}NO_2^-)CH_3$. An excess of nitroethane will lower the concentration of this ion by affecting the equilibrium (II). The result is to decrease the yield of bis- compound and increase the yield of monoaralkylated product.

The reduction of the dinitro compound, the desired product, can be effected in any of the conventional ways, but high-pressure hydrogenation with a Raney nickel catalyst was selected and was found to give good results.

The step of diazotization was carried out according to the directions of Salkowski (3).

Synthesis Number Two

The step of condensing p-methoxybenzaldehyde with nitroethane was previously reported by Alles (1), who allowed the reactants to stand for several weeks using a primary amine as a catalyst. The same reaction was found to be effected quickly by employing methanol as a solvent and refluxing for a few hours. The ketone, p-$CH_3OC_6H_4CH_2COCH_3$, is readily made by the method of Hass and Susie (4), which involves reduction of the nitro olefin with iron and hydrochloric acid. Its oxime was prepared in the usual manner and reduced to the amine by high-pressure hydrogenation, using Raney nickel catalyst. Demethylation was readily accomplished by the method of Woodruff and Conger (6), which consists in heating the methoxy compound, $CH_3OC_6H_4$-$CH_2CHNH_2CH_3$, with concentrated hydrochloric acid under pressure.

EXPERIMENTAL

Synthesis Number One

Preparation of 1-p-nitrobenzylnitroethane. Sodium nitroethane (24.45 g., 0.25 mole) was prepared in the reaction flask by dissolving sodium (5.75 g., 0.25 mole) in a small amount of ethanol, then adding nitroethane (131.2 g., 1.75 moles). p-Nitrobenzyl chloride (42.9 g., 0.25 mole) and 500 ml. of absolute ethanol were added and the mixture was refluxed eleven hours on a steam-bath, during which the solution turned red and a precipitate formed. After filtering, the filtrate was evaporated on a hot plate. The residue was dissolved in benzene and the solution was extracted with sodium bisulfite solution to remove p-nitrobenzaldehyde. (Free p-nitrobenzaldehyde was isolated from this extract, recrystallized and identified.) After removing the benzene, the residue was distilled (b.p. 145–

160° at 0.5 to 0.6 mm.) from a Claisen flask; yield 28 g., 83%. The viscous oil was dissolved in alcohol and crystallized, m.p. 51°.

Anal. Calc'd for $C_9H_{10}N_2O_4$: C, 51.4; H, 4.8; N, 13.0
Found: C, 51.6; H, 4.7; N, 13.0.

The precipitate which had been filtered out was extracted with water to remove sodium chloride (0.24 mole of silver chloride was obtained from the extract upon adding silver nitrate). A grayish residue remained. This melted at 214° after recrystallization from nitrobenzene and was identified as 1,1-bis(*p*-nitrobenzyl)nitroethane.

Anal. Calc'd for $C_{16}H_{15}N_3O_6$: C, 55.67; H, 4.38; N, 12.2
Found: C, 55.48; H, 4.38; N, 12.0.

Preparation of 1-p-aminophenyl-2-propylamine. Distilled 1-*p*-nitrophenyl-2-nitropropane (30 g., 0.142 mole), 150 ml. of absolute ethanol, and 5 g. Raney nickel were placed in a Parr hydrogenation bomb under hydrogen pressure of 1400 lbs./sq. in. at 50–70°. Under these conditions, reduction was complete in one-half hour but at room temperature (25–30°) several hours were necessary for complete reduction

After the pressure had become constant the material was removed, filtered, and the solvent evaporated. The residue was dissolved in hydrochloric acid solution and extracted with benzene to remove the non-basic portions. It was made strongly basic with a large excess of sodium hydroxide (50% solution) and the diamine was extracted with benzene. Benzene was removed and the base was distilled from a Claisen flask; yield 15.6 g., 71%. It was redistilled from a precision column (b.p. 126° at 2 mm., n^{20}_{D} 1.5723, d^{25}_{25} 1.022). The dihydrochloride, obtained by adding excess hydrochloric acid and evaporating, was recrystallized from alcohol-ether. The diamine dihydrochloride is readily oxidized in solution but oxidation can be largely suppressed by using excess acid. The dihydrochloride is a white solid melting above 270°.

Anal. Calc'd for $C_9H_{16}Cl_2N_2$: Cl, 31.80. Found: Cl, 31.86

Preparation of 1-p-hydroxyphenyl-2-propylamine hydrochloride. The procedure of Salkowski (3) was followed. The reaction does not proceed very smoothly and a considerable amount of a brownish by-product results. 1-*p*-Aminophenyl-2-propylamine dihydrochloride (30.17 g., 0.135 mole), 60 ml. of concentrated hydrochloric acid, and 20 ml. of water were mixed and cooled to −3°. Sodium nitrite (9.6 g., 0.139 mole), in 40 ml. of water, was slowly added with adequate stirring. A temperature of 3° or less was maintained throughout the reaction. Agitation was continued for one hour after all the sodium nitrite was added, then the temperature was gradually raised to 70° and was maintained at 70–90° until the evolution of nitrogen ceased. The resulting red solution was extracted with benzene to remove non-basic impurities, and the water layer was evaporated. The gummy, brown residue was dissolved in alcohol, the sodium chloride which precipitates was filtered off, and a large excess of ether was added. The yellow precipitate dissolved in hydrochloric acid with a marked darkening in color, and on cooling, 10–12 g. (40–50%) of a solid separated, m.p. 171–172° after three recrystallizations from concentrated hydrochloric acid. A mixture with a known sample melted at 171–172°. The free amine, prepared from the salt by treating it with concentrated ammonia, was recrystallized from benzene, and melted at 125°. [Mannich and Jacobson (2) have reported 125–126°]. A mixture with an authentic sample melted at 125°.

Anal Calc'd for $C_9H_{14}ClNO$· Cl, 18.93. Found: Cl, 19.14.

Synthesis Number Two

Preparation of 1-p-methoxyphenyl-2-nitropropene. A mixture of *p*-methoxybenzaldehyde (anisaldehyde, 27.2 g., 0.2 mole) and nitroethane (15.0 g., 0.2 mole) in 35 ml. of absolute alcohol and 4.0 ml. of butylamine was refluxed six hours. After cooling in ice and salt, filtering, concentrating, and cooling again, a total of 20 g. (51.8% conversion) was obtained; 3 g. of additional nitro olefin and 9 g. of *p*-methoxybenzaldehyde were recovered by distilling the filtrate. The product melts at 43–44°, conversion 59.6%, yield 87.2%.

Preparation of 1-p-methoxyphenyl-2-propanone. A mixture of 1-*p*-methoxyphenyl-2-nitropropene (96.5 g., 0.5 mole), iron filings (40 mesh, 200 g.), 500 ml. of water, and 1 g. of ferric chloride was refluxed for eight hours with good agitation, and 90 ml. of concentrated hydrochloric acid was added in the course of the eight hours. The mixture was steam distilled until four liters of water had been collected. The distillate was extracted with ether. Upon distillation, the extract provided 48 g. of 1-*p*-methoxyphenyl-2-propanone, b.p. 117–122° at 5 to 6 mm.; yield 59%.

Preparation of 1-p-methoxyphenyl-2-propanone oxime. An alcoholic solution containing 1-*p*-methoxyphenyl-2-propanone (21 g., 0.128 mole) was mixed with an aqueous solution containing hydroxylammonium chloride (21 g., 0.30 mole). After adding sufficient sodium hydroxide (20% solution) to render the mixture just basic, it was refluxed five minutes, precipitated by adding water and cooling. The oxime (20 g., yield 87%) was a mixture of syn- and anti- isomers, m.p. 56–61°.

Preparation of 1-p-methoxyphenyl-2-propylamine. 1-*p*-Methoxyphenyl-2-propanone oxime (42 g., 0.234 mole), 300 ml. of 95% ethanol, and 5 g. of Raney nickel in a Parr hydrogenation bomb were subjected to an initial hydrogen pressure of 1940 lbs./sq.in. Approximately two hours were required for complete reduction. 1-*p*-Methoxyphenyl-2-propylamine was formed. The hydrochloride m. 208°. The yield was 30 g. of pure amine (78%).

Preparation of 1-p-hydroxyphenyl-2-propylamine. The method of Woodruff and Conger (6) was used to split the ether. 1-*p*-Methoxyphenyl-2-propylamine hydrochloride (7 g., 0.034 mole) and 25 ml. concentrated hydrochloric acid were heated in a Carius tube at 140–160° for two hours. The brown, solid residue remaining after evaporation of the acid was dissolved in alcohol, decolorized with Norit, and precipitated by adding ether. 1-*p*-Hydroxyphenyl-2-propylamine hydrochloride, m.p. 171–172°, resulted; yield 5.5 g. (80%).

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SUMMARY

Two syntheses for 1-*p*-hydroxyphenyl-2-propylamine (Paredrine) are described. One synthesis utilizes *p*-nitrobenzyl chloride and a salt of nitro ethane; the other employs *p*-methoxybenzaldehyde (anisaldehyde) and nitroethane as initial materials. Among the intermediates and by-products there are three new compounds, namely, 1-*p*-nitrophenyl-2-nitropropane, 1,1-bis(*p*-nitrobenzyl)-1-nitroethane, and 1-*p*-aminophenyl-2-propylamine.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

SYNTHESIS OF 2-AMINO-1-PHENYL-1-PROPANOL AND ITS METHYLATED DERIVATIVES[1]

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Ephedrine is obtained commercially not only from extraction of the herb mahuang but also by a synthetic process (1) in which *l*-1-hydroxy-1-phenyl-2-propanone, obtained by action of benzaldehyde on fermenting sugar solutions, is allowed to react with methylamine, and the resulting Schiff base is reduced to *l*-ephedrine. This process has the advantage that no resolution is necessary.

Propadrine hydrochloride, also called Mydriatine, is a racemic mixture, melting at 190–194°. It is a mydriatic, diaphoretic, vasoconstrictor, and is used like ephedrine hydrochloride or ephedrine sulfate but its action is more prolonged.

In 1929, Nagai and Kanao (4) reported the synthesis of ephedrine from benzaldehyde and nitroethane. A similar series of reactions has been used in this work and offers a route to ephedrine.

$$\text{(I)}\ C_6H_5CHO + C_2H_5NO_2 \rightarrow C_6H_5CHOHCHNO_2CH_3\ \text{(Two Racemic Forms)}$$

$$\text{(II)}\ C_6H_5CHOHCHNO_2CH_3 + H_2 \xrightarrow{\text{Raney Ni}} C_6H_5CHOHCHNH_2CH_3$$

$$\text{(III)}\ C_6H_5CHOHCHNH_2CH_3 + HCHO\text{, then } + H_2 \xrightarrow{\text{Raney Ni}} C_6H_5CHOHCH(NHCH_3)CH_3$$

The nitro alcohol was obtained in good yield by the method of Vanderbilt and Hass (5), Kamlet (3), and Nagai and Kanao (4), but the method of Kamlet is particularly desirable because of the speed of the reaction. This method involves reaction between nitroethane and the sodium bisulfite addition product of benzaldehyde. It requires only a few hours whereas the other methods require several days.

The unmethylated amino alcohol was obtained by reduction of the nitro alcohol either with zinc and sulfuric acid, tin and hydrochloric acid, sodium amalgam and acetic acid, or by catalytic hydrogenation. Presumably many of the ordinary metal-acid reducing agents can be used provided the temperature is kept sufficiently low to prevent dehydration. There are, however, several by-products of the reduction. When catalytic hydrogenation was selected as the method, N-ethylbenzylamine was a by-product. It presumably forms by the following reactions:

$$\text{(I)}\ C_6H_5CHOHCHNO_2CH_3 \rightleftarrows C_6H_5CHO + C_2H_5NO_2$$

$$\text{(II)}\ C_2H_5NO_2 + H_2 \xrightarrow{\text{Raney Ni}} C_2H_5NH_2$$

$$\text{(III)}\ C_6H_5CHO + C_2H_5NH_2 \rightarrow C_6H_5CH{:}NC_2H_5$$

$$\text{(IV)}\ C_6H_5CH{:}NC_2H_5 + H_2 \xrightarrow{\text{Raney Ni}} C_6H_5CH_2NHC_2H_5$$

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[1] A portion of the doctoral thesis of Fred W. Hoover.

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This series of reactions postulates the formation of benzaldehyde and nitroethane by decomposition of 2-nitro-1-phenyl-1-propanol. It seemed logical to assume that this reaction was brought about by the catalytic effect of the basic (amine) reduction products. This hypothesis is supported by the fact that use of carbon dioxide in the Parr bomb reduces the yield of N-ethylbenzylamine to negligible quantities. Of those tested, the two best methods of reduction, from the standpoint of both simplicity and yield, are that using zinc and sulfuric acid, and that using acetic acid and sodium amalgam.

The amino alcohol which is an intermediate in the formation of Propadrine is easily methylated by adding an equimolecular amount of aqueous formaldehyde and then reducing catalytically.

Each step in the synthesis provides good yields. Efforts to separate the diastereoisomers were much less satisfactory. The method of Nagai and Kanao (4) for resolving the hydrochloride of 2-amino-1-phenyl-1-propanol, using absolute ethanol as the solvent, proved very inefficient, although enough of the desired diastereoisomer, *dl*-nor-ephedrine hydrochloride, was obtained for identification. The pressor action of these four stereoisomers has been studied by Jarowski and Hartung (2).

EXPERIMENTAL

Preparation of 2-nitro-1-phenyl-1-propanol. (a) Method of Vanderbilt and Hass (5). Benzaldehyde (13.25 g , 0.125 mole), nitroethane (9.38 g., 0.125 mole), and 50 ml. of 95% ethanol were mixed, and 2 ml. of sodium hydroxide (25% solution) was added with cooling. After allowing the mixture to stand for four days, the sodium hydroxide was neutralized and most of the alcohol was removed under reduced pressure. The residue was dissolved in ether, extracted with sodium bisulfite solution to remove unreacted benzaldehyde, and then distilled (b.p. 120–130° at 2 to 4 mm.) conversion 28 g. (62%). Based on the benzaldehyde that reacted, the yield was almost quantitative.

(b) Method of Nagai and Kanao (4). Benzaldehyde (106 g., 1 mole), nitroethane (75 g., 1 mole), and 50 ml. of saturated sodium bicarbonate solution were vigorously stirred for one week at room temperature (25–30°). The organic and aqueous layers were separated, the organic layer was washed with sodium bisulfite solution and distilled (b.p. 120–130° at 2 to 4 mm.), 90.5 g. resulted, conversion 50%, yield, based on benzaldehyde which reacted, 90%.

(c) Method of Kamlet (3). Benzaldehyde (106 g., 1 mole) was vigorously agitated with sodium bisulfite (110 g., 1.06 mole) in 500 ml. of water until the formation of the addition compound was complete. Simultaneously, nitroethane (82.5 g., 1.10 mole) was dissolved in a solution made from sodium hydroxide (45 g., 1.125 moles) dissolved in 200 ml. of water. This solution was gradually added, with agitation and at room temperature, to the addition product of benzaldehyde and sodium bisulfite. After stirring for a half hour, the mixture was allowed to stand overnight. The lower layer was discarded and the upper layer was dissolved in ether and washed with sodium bisulfite solution. The ethereal solution was dried over Drierite, and after removal of ether, distilled (b.p. 120–130° at 2–4 mm.) The usual conversion is 90–100 g. (50–55%) and the yield, based on benzaldehyde which reacts, is nearly quantitative.

Preparation of 2-amino-1-phenyl-1-propanol. (a) With zinc and sulfuric acid. Sulfuric acid (375 g. of 30% acid) was added with stirring to a mixture of 2-nitro-1-phenyl-1-propanol (54.3 g., 0.3 mole), zinc dust (90 g., 1.37 mole of 80 mesh zinc), and 100 ml. of 95% ethanol. The acid was added at such a rate that the temperature remained at 45° or below. Usually 10 to 12 hours were required. Agitation was continued for 1–2 hours after completing the addition of acid, then after extracting the acidic solution with ether to remove non-basic materials, a large excess of sodium hydroxide (as 50% solution) was added. The product which was freed was extracted with ether. Three extractions, with a total of 500 ml. of ether, sufficed. The ether solution was dried, ether was removed, and the product was distilled (b.p. 122° at 4 to 5 mm.); 29–32 g. resulted (yield 65 to 70%). The viscous liquid solidified on standing, and m. 46–50°.

Anal. Calc'd for $C_9H_{14}ClNO$: Cl, 18.91. Found: Cl, 18.88.

(b) With sodium amalgam and acetic acid. Glacial acetic acid (160 g., 2.66 moles) and 3% sodium amalgam (1924 g., 2.5 moles) were added in small portions and with good agitation to a solution of 2-nitro-1-phenyl-1-propanol (36.2 g., 0.2 mole) in 300 ml. of absolute alcohol. Acetic acid was introduced at a rate sufficient to maintain an acidic reaction. The rate of adding the amalgam was such that the temperature was maintained at 45° or less. At the end of the reaction mercury was separated, water was added to dissolve the sodium acetate, and the mixture was heated to remove the alcohol and concentrate the solution. The cooled solution was extracted with ether to remove non-basic material and then treated with excess sodium hydroxide (as 50% solution), and the product was taken up in ether. After removing the ether and distilling, 18–21 g. of product resulted (b.p. 112° at 2 to 3 mm.).

(c) Catalytic hydrogenation. A mixture of 2-nitro-1-phenyl-1-propanol (36.2 g., 0.2 mole), 100 ml. of absolute alcohol, and 4 g. of Raney nickel was placed in a Parr hydrogenation bomb. Sufficient solid carbon dioxide was added to produce a pressure of 300 lbs./sq. in., then hydrogen was introduced to bring the total initial pressure to 1800 lbs./sq.in. Approximately four hours was required for complete reduction. On distilling, N-ethylbenzylamine (5%) and 2-amino-1-phenyl-1-propanol (87%) were obtained. When no carbon dioxide was used, the yield of N-ethylbenzylamine approximated 45%.

N-ethylbenzylamine was identified by its boiling point (198°) and the melting point of the hydrochloride (184°) compared with an authentic sample prepared from benzaldehyde and ethylamine.

Identification of 2-amino-1-phenyl-1-propanol. The product was a very viscous, colorless liquid which solidified on standing, m.p. 46–50°. When dry hydrogen chloride was passed into an ether solution, a gelatinous precipitate resulted, which hardened on standing. This character of precipitate was attributed to the rather complex mixture of isomers, since an authentic sample of *l*-ephedrine yielded well formed crystals. A better product could be made from the base by treating it with concentrated hydrochloric acid to the end point of methyl red indicator, evaporating under reduced pressure, and recrystallizing from butanol-ether (50–50 mixture by volume). The white crystals (m.p. 134–137°) gave 18.87 and 18.89% chlorine by Fajan's method (theory 18.91%). The neutral equivalent of the free amine was 155 (theory 151). The material is therefore believed to be a mixture of *dl*-norephedrine and *dl*-norisoephedrine. These two compounds are diastereoisomers and have the following constants:

	dl-norephedrine	*dl*-norisoephedrine
Free base	m.p. 104–105°	m.p. 71°
Hydrochloride	m.p. 192°	m.p. 169°

After four fractional crystallizations from absolute alcohol it was possible to obtain a hydrochloride m.p. 192°. The melting point of a mixture of this compound and norephedrine hydrochloride was 192°. Thus, it is possible to separate the components of the mixture by fractional crystallization but the yield is low.

The method of Nagai and Kanao (4), which utilizes the greater solubility in ether of norisoephedrine to separate the isomers, was tried on the free base. After four crystallizations, the amino alcohol melted at 72–75°. Since the original base mixture melted at 46–50°, the difference in solubility is evidently not great.

The mixture of stereoisomers obtained in this synthesis was tested for physiological action by two manufacturers of pharmaceuticals who compared it with norephedrine hydrochloride and found it to have a similar effect on the blood pressure. The work of Jarowski and Hartung already has been mentioned (2).

Preparation of 2-methylamino-1-phenyl-1-propanol. Formaldehyde (0.3 mole of active material as 37% solution) was added, with cooling, to 2-amino-1-phenyl-1-propanol (45.3 g., 0.3 mole) dissolved in ethanol. After the mixture had stood for a half hour, the Schiff base was reduced in a Parr hydrogenation bomb. Raney nickel (4 g.) was used as a catalyst. Initial pressures of hydrogen from 600 to 1400 lbs./sq.in. were suitable. The product was recovered by distilling the alcoholic solution with a Podbielniak column. There was a small amount of material which boiled at 106° at 5 mm., but the main portion of the distillate was collected at 115–120° at 5 mm. The yield of the more high-boiling product was 40 g. (81%).

Anal. Calc'd for $C_{10}H_{15}NO$: N, 8.5. Found: N, 8.4.

This mixture presumably is norephedrine and norisoephedrine and their monomethylated derivatives. This type of alkylation usually results in the formation of primary, secondary, and tertiary amines. Knowing that they usually result in such mixtures, we assume that small amounts are present in spite of the good agreement of the percentage of nitrogen with that required for $C_{10}H_{15}NO$. Samples of this material were prepared for several laboratories which specialize in techniques for separating isomers, but as yet no satisfactory process has been devised.

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SUMMARY

The synthesis of 2-amino-1-phenyl-1-propanol and of 2-methylamino-1-phenyl-1-propanol has been effected in several ways, all utilizing economical intermediates as initial materials. The mixture of diastereoisomers can be obtained in good yield but the methods for separating the isomers are not yet entirely satisfactory.

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[Contribution from the School of Chemistry, Rutgers University]

THE REACTION OF ETHYLENE OXIDE AND ETHYLENE BROMOHYDRIN WITH *n*-BUTYLMAGNESIUM BROMIDE

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The Organic Syntheses method for the preparation of 1-hexanol involves the addition of ethylene oxide to an ethereal solution of *n*-butylmagnesium bromide (1a). The over-all reaction may be represented by the following equation:

$$C_4H_9MgBr + \underbrace{CH_2CH_2O} \rightarrow C_4H_9CH_2CH_2OMgBr$$

1-Hexanol is, of course, obtained upon hydrolysis of the magnesium salt.

The mechanism suggested by the above equation would be a nucleophilic attack by the carbanion of the Grignard reagent upon one of the carbon atoms of the ethylene oxide:

$$C_4H_9^- + \underbrace{CH_2CH_2O} \rightarrow C_4H_9CH_2CH_2O^-$$

However, such a mechanism does not account for the 2-hexanol which, as was found during the present work, is always one of the reaction products.

Evidence has been obtained by Huston and Agett (and by others whose work is reviewed by these authors) that the insoluble product of the reaction between one mole of ethylene oxide and one mole of alkylmagnesium bromide is the same as that obtained by passing the oxide into an etheral solution of magnesium bromide. The insoluble product may be represented by the empirical formula $C_4H_8Br_2MgO_2$ (2). This material reacts with the dialkylmagnesium upon heating to yield magnesium bromide and the condensation product.

It has long been known that, when one mole of ethylene oxide is passed into one mole of Grignard reagent at room temperature or below, the main product obtained upon hydrolysis of the unheated solution is an ethylene halohydrin.

The structure of the ethylene oxide-magnesium bromide complex is unknown. Earlier workers favored $(BrCH_2CH_2O)_2Mg$, but according to Huston and Agett about half the bromine is ionic (2). It may be imagined that the structure is $BrCH_2CH_2OMgBr \cdot \underbrace{CH_2CH_2O}$. Whatever the structure, condensation of this material with the dialkylmagnesium may involve to some extent the nucleophilic reaction mentioned previously, but most probably involves the following reaction to a greater extent:

$$C_4H_9^- + BrCH_2CH_2O^- \xrightarrow{\Delta} C_4H_9CH_2CH_2O^- + Br^-$$

Neither of these nucleophilic reactions should give rearrangement (3).

Two pieces of evidence found during the present work support a theory that the $BrCH_2CH_2O^-$ particle may, upon heating, lose a bromide ion (perhaps as a result of an electrophilic attack by magnesium) and then rearrange to acetaldehyde.

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1. A violent reaction which occurred during the reaction of *n*-butylmagnesium bromide with ethylene bromohydrin resulted in a much higher yield of 2-hexanol than was obtained in a similar experiment in which the violent reaction did not take place.

2. The product of the reaction between ethylene oxide and magnesium bromide underwent a further violent reaction when heated in a bomb. The product of the final reaction appeared to be an acetaldehyde resin. In a parallel experiment, acetaldehyde gave a similar resin, but no violent reaction.

The possibility of the formation of acetaldehyde by dehydrobromination of the $BrCH_2CH_2O^-$ particle under the influence of the proton acceptor RO^- (or R^-) cannot be ignored:

$$(BrCH_2CH_2O)^- + RO^- \longrightarrow ROH + (BrCH_2CHO)^=$$
$$(BrCH_2CHO)^= \longrightarrow Br^- + (CH_2CHO)^-$$
$$(CH_2CHO)^- + ROH \longrightarrow CH_3CHO + RO^-$$

However, it is to be expected that the removal of a second proton from ethylene bromohydrin could be accomplished only with such difficulty (*cf.* the second ionization of a dibasic acid) that such a mechanism seems unlikely.

Preparation of 1-hexanol. 1-Hexanol was prepared by the reaction of ethylene oxide with *n*-butylmagnesium bromide in 65% yield, and by the reaction of ethylene bromohydrin with the same Grignard reagent in 51% yield. 2-Hexanol constituted 13.4% of the total hexanols obtained in the former preparation, and 10.1% in the latter.

The yield of 1-hexanol in the reaction of ethylene oxide with dibutylmagnesium at 0–15° was 44%, with only 1.84% of the hexanols being 2-hexanol.

Since both condensations with *n*-butylmagnesium bromide are known to involve the ethylene bromohydrin salt, it was to be expected that the amount of rearranged material would be about the same in both reactions.

The reaction of ethylene oxide with dibutylmagnesium involves a nucleophilic attack of the carbanion upon a carbon atom of the oxide. Such a reaction should give no rearrangement. Since there is little evidence that ethylene oxide should rearrange under the conditions of the condensation, no 2-hexanol was expected in this reaction. The 1.84% 2-hexanol isolated may represent acetaldehyde present in the reagents despite every effort to remove it, or it may have been produced by unknown side reactions.

The "violent" reactions. The vigorous reaction which may set in during the reaction between ethylene oxide and *n*-butylmagnesium bromide is well known, and adequate warning as to precautions to prevent it are given in Organic Syntheses (1a). Since this reference attributes the vigorous reaction to the rearrangement of an oxonium-type complex of ethylene oxide, a similar reaction was not anticipated with ethylene bromohydrin. One reaction mixture was heated with considerably less care than that employed with ethylene oxide, and the resulting vigorous reaction forced some of the mixture through the reflux condenser. The yield of 1-hexanol actually recovered was 38% and it was estimated that approximately one-fifth of the reaction mixture was lost. However, 22.8% of the total hexanols recovered was 2-hexanol, in contrast to 10.1% 2-hexanol in a similar reaction in which the violent reaction did not take place.

It seems probable that the violent reaction mentioned in Organic Syntheses may involve the transition of the magnesium salt of ethylene bromohydrin to acetaldehyde. The statement is made in Organic Syntheses that the yield of 1-hexanol will be low if the violent reaction is allowed to take place.

Other examples in which an oxide reacts with the Grignard reagent to a greater or lesser extent as though it were a carbonyl compound are known. Styrene oxide reacts as though it were phenyl acetaldehyde (4) and 2,3-epoxybutane reacts as though it were butanone (5). An instance of the isolation of an aldehyde monomer after the treatment of an oxide with magnesium bromide etherate has been reported (6).

EXPERIMENTAL

Preparations of 1-hexanol were carried out essentially according to the directions of Organic Syntheses (la), except that refluxing at 35° was continued for five hours instead of one.

The products were separated by Snyder columns into fractions distilling in the following ranges: (a) below 136°, (b) 136–140°, (c) 140–154°, (d) 154–157°. The 154–157° fraction was assumed to be 1-hexanol. The 140–154° fraction usually amounted to considerably less than 1% of the 1-hexanol. The 136–140° fractions were identified as 2-hexanol by the 3,5-dinitrobenzoate and the *alpha*-naphthylurethan.

The melting points of the 3,5-dinitrobenzoates from all the experiments fell within the range 37.0–38.2°. Previous values given are 38.6° (7) and 38° (8a).

The *alpha*-naphthylurethans were heavy oils which could not be recrystallized in the usual fashion. An isothermal recrystallization was carried out as follows: The yellow oil was dissolved in about ten volumes of 95% alcohol. To this, water was added dropwise until approximately half of the oil had reprecipitated. This oil extracted the yellow material from the alcohol solution. The clear solution was transferred to another flask and an equal volume of water was added rapidly. The milky supernatant liquid was decanted from any oil which formed in five minutes, and set aside at room temperature. After 24 hours the voluminous, white, crystalline precipitate was filtered off and air dried.

The urethans melted in the range 59.3–60.5°. Previous values given are 60.5° (9) and 58-62° (9).

All reagents were tested for acetaldehyde with a supersensitive Schiff reagent (10) by visual comparison with known standards consisting of acetaldehyde in water. Acetaldehyde contents estimated in this manner were as follows: benzene, dioxane, and *n*–butyl bromide: 0.000%; ethylene bromohydrin: 0.013%; the ether used in the vigorous reaction between ethylene bromohydrin and *n*-butylmagnesium bromide: 0.04%; and the ether used in all other preparations of 1-hexanol: 0.006%. However, more significance was attached to the fact that no 2-hexanol (or other material boiling above 118°) could be found in the products from the preparation and hydrolysis of *n*-butylmagnesium bromide in an aliquot portion of the ether used in the preparations of 1-hexanol.

"Blank" preparation. A large batch of about fifteen liters of anhydrous ether was kept over powdered potassium hydroxide for several months prior to use. Portions of this ether were used in this reaction and in the next three preparations to be described.

n-Butylmagnesium bromide was prepared from 297 g. (2.17 moles) of *n*-butyl bromide in 3,650 ml. of ether and 53 g. (2.32 atoms) of magnesium. After hydrolysis, the reaction mixture was treated according to the Organic Syntheses directions for working up 1-hexanol.

There were obtained 28.2 g. of material boiling between 80 and 118°, mostly benzene and *n*-butanol, and a negligible amount of material boiling above 118°.

Failure to isolate any 2-hexanol from this experiment was taken to indicate that the amount of acetaldehyde present in the ether was insufficient to account for the 2-hexanols found in the experiments in which ether from this same batch was used.

Reaction of ethylene oxide with n-butylmagnesium bromide. This reaction was carried out essentially according to the Organic Syntheses procedure for the preparation of 1-hexanol. The ethylene oxide was passed through two or three tubes connected in series (2.5 cm. in diameter, 150 cm. over-all length) packed with freshly powdered potassium hydroxide, to remove acetaldehyde, then directly into the reaction mixture. The brown acetaldehyde polymer formed only in the first 25 cm. or so of the first tube. Ethylene oxide thus treated gave a negative test with ordinary Schiff reagent.

The tubes had to be watched carefully for the development of unpredictable "hot spots" which indicated that the ethylene oxide was polymerizing in that region. A tube was replaced with a fresh one whenever a "hot spot" was detected, to keep the losses of ethylene oxide due to polymerization to a minimum.

The Grignard reagent was prepared from 827 g. (6.04 moles) of *n*-butyl bromide in 2,000 ml. of ether (from the batch, a portion of which was used in the previous experiments) and 153 g. (6.30 atoms) of magnesium, and 300 g. (6.80 moles) of ethylene oxide were added. There were obtained 400 g. (65.0% yield) of 1-hexanol and 61.9 g. of 2-hexanol.

Reaction of ethylene bromohydrin with n-butylmagnesium bromide. The procedure was essentially that used in the previous experiment except, of course, two moles of Grignard reagent had to be used because one was destroyed by the active hydrogen of the bromohydrin.

The Grignard reagent was prepared from 1,430 g. (10.42 moles) of *n*-butyl bromide in 3,600 ml. of ether (from the batch, portions of which were used in the previous experiments) and 260 g. (10.70 atoms) of magnesium. To this was added dropwise 650 g. (5.20 moles) of ethylene bromohydrin under the same conditions used for the addition of ethylene oxide in the previous experiment.

The bromohydrin was prepared according to the directions of Organic Syntheses (1b) and was distilled twice, the fractions collected being: 48.0–57.3° at 9.2–10.4 mm. and 49.6–50.0° at 5.5–5.9 mm. The bromohydrin was analyzed for bromine by the sodium in alcohol method (8b).

Anal. Calc'd for C_2H_5BrO: Br, 63.95. Found: Br, 63.88, 63.99, 64.00.

The yield of 1-hexanol was 268 g. (50.6%) and that of 2-hexanol was 30.0 g.

Reaction of ethylene oxide with dibutylmagnesium. The ether used was from the batch, portions of which were used in the previous preparations.

Dibutylmagnesium was prepared from the Grignard reagent by precipitation of the halogen-containing compounds with dioxane. Dioxane was added to the Grignard solution with vigorous stirring at room temperature, at a rate such that no refluxing took place.

The condensation step of the reaction was carried out in two separate batches. In the first 597 g. (6.78 moles) of dioxane freshly distilled from bright sodium was added to 5.01 moles of *n*-butylmagnesium bromide in 1,600 ml. of ether. In the second 772 g. (8.77 moles) of dioxane was added to 6.04 moles of Grignard solution in 2,600 ml. of ether.

The precipitates were not separated from the dibutylmagnesium solutions. Instead, the yields of dibutylmagnesium were estimated by the preparation of a third, smaller batch in which 61.6 g. (0.70 moles) of dioxane was added to 0.50 moles of Grignard solution in 300 ml. of ether. The mixture was centrifuged and 258 ml. of solution containing 1.232 mmol. Mg./ml. were decanted. The precipitate was stirred with fresh ether, centrifuged until the precipitate occupied the same volume as before, and 319 ml. of solution containing 0.1699 mmol. Mg./ml. was decanted.

In the following equation, X is the volume of solution entrapped in the precipitate:

$$X \cdot 1.232 = (319 + X)\ 0.1699$$

$$X = 51 \text{ ml.}$$

$$(258 + 51) \cdot 1.232 = 380.5 \text{ mmol. Mg.}$$

The yield of dibutylmagnesium is thus 76.1%, and it was estimated that the first batch contained 1.90 moles, and the second 2.30 moles, of dibutylmagnesium. To the first was added 200 g. (4.53 moles), and to the second was added 300 g. (6.80 moles) of ethylene oxide, purified and added as described previously.

The mixtures were hydrolyzed with distilled water after standing for eight hours at 0–15°. After hydrolysis was complete, the magnesium hydroxide was dissolved in dilute sulfuric acid, the mixtures were combined and worked up together.

The yield of 1-hexanol was 373 g. (43.5%) and that of 2-hexanol, 7.0 g.

A vigorous reaction between ethylene bromohydrin and n-butylmagnesium bromide. The reaction was carried out as the previously described condensation between these reagents except that the refluxing at 35° was for only one and a half hours instead of five. When part of the ether was replaced with benzene and the temperature raised to about 65°, a vigorous reaction set in which forced about one-fifth of the material through the reflux condenser.

This Grignard reagent was prepared from 250 g. (10.33 atoms) of magnesium and 1,370 g. (10.00 moles) of *n*-butyl bromide, in 3,840 ml. of ether which was estimated to contain 0.04% acetaldehyde, as has been described.

The bromohydrin used was distilled three times, the fractions collected being: 50–77° at 23.5 mm., 46.0–48.0° at 4.2–4.8 mm., and 48–49° at 3.0–3.1 mm. The bromohydrin was analyzed for bromine by the sodium in alcohol method (8b).

Anal. Calc'd for C_2H_5BrO: Br, 63.95. Found: Br, 63.78, 63.89, 63.78.

There were obtained 184 g. (38.0%) of 1-hexanol and 54.6 g. of 2-hexanol.

Reactions of acetaldehyde with n-butylmagnesium bromide These reactions were carried out to determine if the vigorous refluxings or other steps in the procedure involved in the preparation of 1-hexanol might destroy or in some manner cause the loss of appreciable amounts of 2-hexanol.

Two simultaneous preparations were carried out as follows, portions of the same reagents being used for each:

One hundred grams (0.73 mole) of *n*-butyl bromide in 300 ml. of ether was added to 18.5 g. (0.76 atom) of magnesium. The Grignard solution was cooled to −5° and the addition of 50 g. (1.14 moles) of acetaldehyde in 300 ml. of cooled ether was begun. The temperature was maintained at −10 to −5° and the acetaldehyde was added over an hour and a half.

One solution was allowed to stand at room temperature for ten days. At the end of this time the mixture was hydrolyzed, and the oily layer was separated. The water layer was thoroughly extracted with ether. The combined ether extracts were fractionally distilled. The yield of 2-hexanol was 34.4 g. (46.2%).

The second solution was treated exactly according to the method previously described for the preparation of 1-hexanol from ethylene oxide and *n*-butylmagnesium bromide. The yield of 2-hexanol was 38.7 g. (52.0%).

These experiments demonstrate that appreciable loss of 2-hexanol in the previous experiments is unlikely.

Resinification of ethylene oxide. The anhydrous magnesium bromide solution was prepared by the addition of 188 g. (1.18 moles) of bromine (dried by shaking with concentrated sulfuric acid) to 28.5 g. (1.18 moles) of magnesium in 1,000 ml. of ether.

The mixture (two layers) was cooled to below 10° and the addition of 100 g. of ethylene oxide was started. The ethylene oxide was passed through a tube, 2.5 cm. in diameter, packed with 20 cm. of 8 mesh soda-lime, and then as a gas directly into the magnesium bromide. The oxide was readily absorbed at all times, although the temperature rose somewhat above 10°.

The mixture stood for fifteen hours at room temperature, and finally was refluxed for four hours. Part of the ether was distilled off, replaced with benzene, and refluxing at 65° was continued for three hours, during which most of the precipitate dissolved.

Half of this material was placed in a steel bomb fitted with a themocouple and a pressure guage. The temperature was raised to 84° and held there for half an hour, with vigorous shaking. This treatment appeared to effect no change in the solution.

The second half of the solution was heated as before except that the temperature was raised to 95° at the rate of about 0.8° per minute, at which temperature a violent reaction set in as evidenced by a sudden, sharp increase in temperature and pressure. Heating was discontinued as soon as the reaction set in, but the temperature had reached a maximum in 3 minutes 8° above that expected, and the pressure had increased from twenty-one pounds at the start of the vigorous reaction to thirty-three pounds at the maximum. The product of this reaction was a dark brown resin with the characteristic caramel-like odor noted when acetaldehyde is treated with concentrated alkali.

The resin washed successively with dilute potassium hydroxide and dilute hydrochloric acid contained 62.3% C, 7.1% H and 2.0% Br.

Resinification of acetaldehyde. The anhydrous magnesium bromide solution was prepared from 160 g. (2.00 moles) of bromine, 25 g. (1.03 atoms) of magnesium, and 700 ml. of ether. The upper layer of the solution was discarded. One-half of the lower layer plus an equal volume of benzene was used for each of the following preparations.

Acetaldehyde was not readily absorbed by the cooled magnesium bromide solution, so the liquid acetaldehyde (22 g., 0.5 mole) was added to the cooled material in the bomb. The temperature was raised as before except there was no sudden increase in temperature or pressure at any time, therefore the temperature was raised to 110° and held there for an hour. The product of this reaction was identical in odor with the resin from ethylene oxide, but was somewhat softer and darker in color. The resin contained 62.9% C and 7.9% H.

Particular care was taken to insure the absence of magnesium metal in the above reaction mixture In the second preparation in which 5 g. of magnesium turnings was added to the mixture the product could not be distinguished from the first by appearance or odor. The resin contained 59.6% C and 7.2% H.

A solution consisting of 24 g. of acetaldehyde in 200 ml. of ether and 200 ml. of benzene was heated at 110° with no change in the appearance of the solution except for a very slight discoloration. The material was completely volatile on the steam-bath except for a trace of yellowish residue.

The resins from ethylene oxide and acetaldehyde were all insoluble in water and dilute acids and bases, very slightly soluble in benzene and aliphatic hydrocarbons, partially soluble in the lower alcohols, and completely soluble in chloroform. Because the composition of these resins is dependent upon the degree of dehydration, and therefore may vary widely (11), little significance was attached to elemental analyses. More dependence was placed upon the characteristic odor, the solubility characteristics, and the general appearance of the resin.

The carbon and hydrogen determinations reported in this paper were run by Mr. M. J. Gardella.

SUMMARY

Evidence is presented which supports the theory that the anion of the magnesium salt of ethylene bromohydrin may rearrange in part during the reaction of ethylene oxide with alkylmagnesium bromides, giving rise to products which must have come from acetaldehyde.

New Brunswick, N. J.

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[Contribution from the Research Laboratory of Armour and Company]

SOLUBILITIES OF DODECYL- AND OCTADECYL-TRIMETHYLAMMONIUM CHLORIDES IN ORGANIC SOLVENTS

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The quaternary ammonium salts which contain at least one long-chain hydrocarbon group are rapidly becoming an important class of compounds, many representatives of which have been synthesized within recent years. Such compounds function as cationic colloidal electrolytes when dissolved in water and the electrical conductivities of aqueous solutions of the alkyltrimethylammonium bromides have been studied in detail (1). On the other hand, the literature upon the solubilities of the long-chain quaternary ammonium compounds in organic solvents has been fragmentary and largely confined to qualitative statements concerning specific compounds. When Krafft and Moye (2) first described hexadecyltriethylammonium iodide they reported it to be soluble in warm water and ethanol but insoluble in ether. Later, Reychler (3) observed this compound to be soluble in warm water but almost insoluble in cold water, soluble in ethyl acetate and in ethanol, and insoluble in ether. Recently, Shelton and coworkers (4) have prepared a number of quaternary ammonium salts containing a long-chain hydrocarbon group and have stated that, in general, they are soluble in water and ethanol, sparingly soluble in acetone, and nearly insoluble in diethyl ether.

In an attempt to obtain a broader understanding of the solubility behavior of the long-chain quaternary ammonium salts we have determined the solubilities of two representative compounds of this class, namely, dodecyltrimethylammonium chloride and octadecyltrimethylammonium chloride, in a variety of organic solvents.

EXPERIMENTAL

Preparation of dodecyltrimethylammonium chloride. To a mixture of 0.1 mole (18.5 g.) of dodecylamine (f.p. 28.28°), 12 cc. of water, and 200 cc. of ethanol was slowly added 13.7 cc. of 85% formic acid. After cooling to about 60°, 20 cc. of 36% formaldehyde was added and the reaction was allowed to proceed for two hours at 60–80°. When the evolution of carbon dioxide stopped, the solution was made alkaline with sodium hydroxide and the amine was separated and dried over sodium carbonate. The amine was then fractionated through a two-foot Stedman-packed column. Seven fractions were taken and a freezing point was determined on each fraction. Fractions 2–5 inclusive had the freezing point −20.30° and were combined. The over-all yield was 60%.

The quaternary ammonium salt was prepared by adding methyl chloride to the tertiary amine, mixed with 50 cc. of Skellysolve A (b.p. 35–40°), in a bomb and heating for two hours at 60°. The bomb was opened slowly to permit the gradual escape of methyl chloride and solvent. The product was removed and recrystallized several times from 200 cc. of benzene to which just enough ethanol was added to effect solution. The quaternary ammonium salt was dried and stored in a desiccator. It is slightly hygroscopic.

Preparation of octadecyltrimethylammonium chloride. A procedure similar to the above was employed. The octadecylamine used had the freezing point 52.86° and the dimethyloctadecylamine the freezing point 22.89°. The quaternary ammonium salt is not hygroscopic.

The freezing points of the amines were determined by previously described methods (5). The quaternary ammonium chlorides do not possess definite melting points. They begin to soften at 70° and decompose at 180°. The solubilities of the quaternary ammonium salts were determined in sealed tubes by the method and with the apparatus previously described (6, 7, 8, 9).

RESULTS AND DISCUSSIONS

Since both dodecyl- and octadecyl-trimethylammonium chlorides are true salts one would expect them to be difficultly soluble in the non-polar and in the slightly polar solvents. This study, which comprises the solubility determinations of these two salts in a series of organic solvents of varying polarities, broadly confirms this generalization. Notable exceptions are the appreciable solubility of these quaternary ammonium chlorides in the two chlorinated solvents investigated, chloroform and carbon tetrachloride. The high solubilities in chloroform may possibly be explained by hydrogen bonding between the solute and solvent molecules. Solvation may account for the appreciable solubilities of these salts in carbon tetrachloride, although this phenomenon is most frequently encountered when both solute and solvent are polar substances. Saturated solutions of dodecyltrimethylammonium chloride in carbon tetrachloride form gels above 45°, and this salt could not be induced to crystallize from chloroform since it forms gels at all the concentrations investigated. The solubility of octadecyltrimethylammonium chloride in chloroform is shown in Curve C, Figure 1, and the solubilities of the two quaternary ammonium chlorides in carbon tetrachloride are shown in Table I.

TABLE I

SOLUBILITIES OF DODECYL- AND OCTADECYL-TRIMETHYLAMMONIUM CHLORIDES IN CARBON TETRACHLORIDE

SALT	G. PER 100 G. SOLVENT						
	30°	40°	45°	50°	55°	60°	65°
Dodecyl-	1.21	34.2	102	gel	—	—	—
Octadecyl-	—	—	—	—	0.402	5.04	36.2

Both dodecyl- and octadecyl-trimethylammonium chlorides are essentially insoluble in *n*-hexane, cyclohexane, benzene, and ethyl acetate. No attempts were made to determine their actual solubilities in these solvents; however, the following observations confirm their limited solubilities. The solubility of dodecyltrimethylammonium chloride is < 0.2 g. in 100 g. of *n*-hexane, <0.3 g. in 100 g. of cyclohexane, < 0.5 g. in 100 g. of benzene, and < 0.39 g. in 100 g. of ethyl acetate, at 95°. Although octadecyltrimethylammonium chloride is soluble in hot benzene, it is only slightly soluble in *n*-hexane and cyclohexane ($< 0.16\%$ and $< 0.3\%$, respectively, at 95°). The solubility of octadecyltrimethylammonium chloride in benzene is shown in Curve B, Figure 1. The greater solubility of this salt in benzene when compared to that of its lower homolog indicates that higher hydrocarbon loading is attended by increased solubility in the non-polar and slightly polar solvents. This may also be illustrated by the comparative solubilities of the two salts in ethyl acetate. The dodecyl quaternary ammonium chloride is insoluble in this solvent as previously stated, whereas the octadecyl quaternary ammonium chloride is somewhat soluble at temperatures above the boiling point of the solvent (1.22 g. in 100 g. at 84°, and 5.04 g. in 100 g. at 86°). The experimental points from which these values were obtained are shown in Curve A, Figure 1.

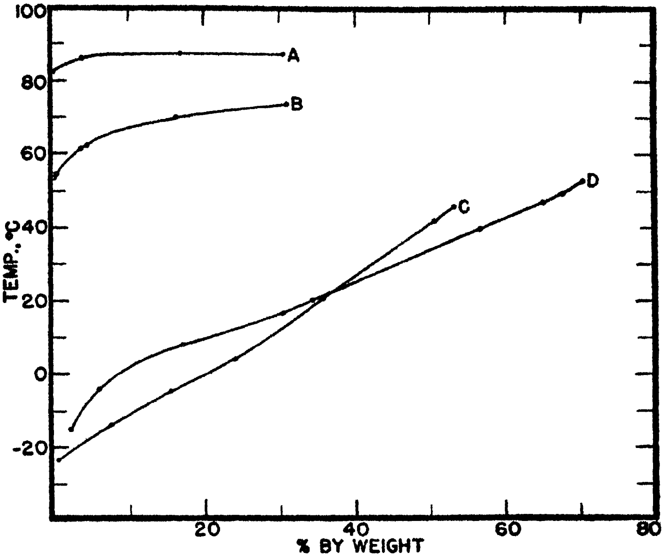

FIG. 1. SOLUBILITIES OF OCTADECYLTRIMETHYLAMMONIUM CHLORIDE IN VARIOUS SOLVENTS

A. Ethyl Acetate, B. Benzene, C. Chloroform, D, 93.5 % Ethanol.

TABLE II

SOLUBILITIES OF DODECYL- AND OCTADECYL-TRIMETHYLAMMONIUM CHLORIDES IN 93.5% ETHANOL, METHANOL, AND ACETONITRILE

SALT	SOLVENT	−40°	−30°	−20°	−10°	0°	10°	20°	30°	40°	50°	60°	70°	80°
Dodecyl-	Methanol	16.0	31.0	35.2	83.1	113.8	145.8	180.0	226.6					
Dodecyl-	Acetonitrile					4.8	10.9	18.2	32.8	81.2				
Octadecyl-	93.5% Ethanol				3.7	9.3	25.6	43.1	82.9	132.3	209.8			
Octadecyl-	Methanol				5.7	15.4	32.5	71.6	112.8	168	252.1			
Octadecyl-	Acetonitrile							0.7	1.8	3.2	5.1	9.9	32.7	78.6

The solubilities of dodecyl- and octadecyl-trimethylammonium chlorides in methanol and of the latter salt in 93.5% ethanol are shown in Table II. It is

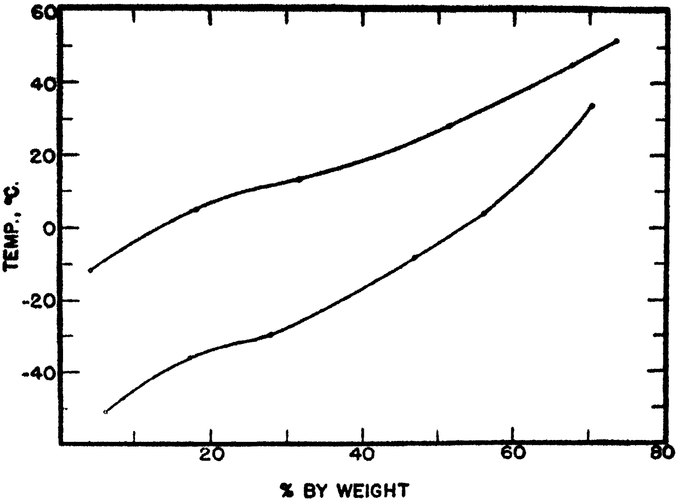

FIG. 2. SOLUBILITIES OF DODECYL- AND OCTADECYL-TRIMETHYLAMMONIUM CHLORIDES IN METHANOL

$C_{12}H_{25}(CH_3)_3NCl$ is the lower curve

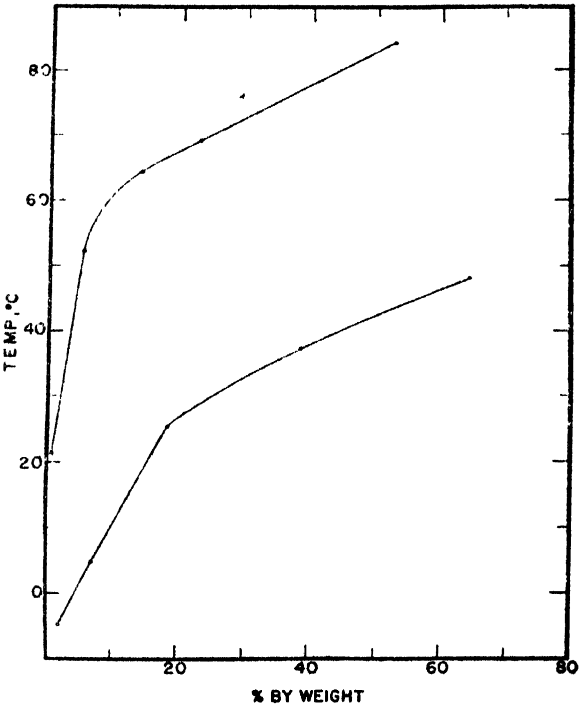

FIG. 3. SOLUBILITIES OF DODECYL- AND OCTADECYL-TRIMETHYLAMMONIUM CHLORIDES IN ACETONITRILE

$C_{12}H_{25}(CH_3)_3NCl$ is the lower curve evident that these salts are more soluble in such solvents than in the less polar solvents with the exception of the chlorinated solvents. They are more soluble in methanol than in acetonitrile, and in both solvents the lower homolog is the more soluble. This is illustrated in Figures 2 and 3, which compare the solubilities of these salts in methanol and acetonitrile, respectively.

The dodecyl quaternary ammonium chloride is appreciably soluble in acetone, whereas the octadecyl quaternary ammonium chloride possesses a limited solubility in this solvent, as shown in Table III.

The fact that these two compounds are salts greatly influences their solubility behavior in organic solvents. Although they are in general much more soluble in polar solvents than in the non-polar or slightly polar solvents, a definite relationship between their solubilities and the polarity of the solvent apparently does not exist. This is evidenced by several of the solubility determinations presented in this paper. The marked tendency to form gels characterizes their behavior in several of the solvents investigated.

TABLE III

SOLUBILITIES OF DODECYL- AND OCTADECYL-TRIMETHYLAMMONIUM CHLORIDES IN ACETONE

SALT	G. PER 100 G. SOLVENT				
	30°	40°	50°	55°	56.5°
Dodecyl-	2.88	9.76	41.75	91.9	110.6
Octadecyl-	—	—	0.503	0.706	0.756

SUMMARY

The solubilities of dodecyltrimethylammonium chloride and of octadecyltrimethylammonium chloride have been determined in *n*-hexane, cyclohexane, benzene, ethyl acetate, carbon tetrachloride, chloroform, acetone, methanol, 93.5% ethanol, and acetonitrile.

CHICAGO 9, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY AND EHRLICH LABORATORY]

EXPERIMENTS IN THE VERATROLE AND QUINOXALINE GROUPS

JACOB EHRLICH AND MARSTON TAYLOR BOGERT

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As one branch of our work in the search for superior antimalarials (1, 2), we have had occasion to study the veratrole and quinoxaline groups, and have found them sufficiently interesting to justify additional exploration, because of the ease with which the 4,5-diamino- and 3,4,5-triamino-veratroles are prepared and the many reactions to which such vicinal polyamines are subject. Further, it is not improbable that prospecting in these fields may uncover compounds of biological or therapeutic significance. Attention is called particularly to recent work in the sulfaquinoxaline field (3–13).

Quinoxaline derivatives have also been studied by others with reference to possible antimalarial activity (14, 15) (S.N. 3078, 5038, 5043, 6593, 7749, 8002, 10080, 10081, 10084, 10085, etc.), but without discovering as yet any very promising compounds.

The antibacterial activity of some quinoxaline derivatives has been explored by O. Schales, S. Schales, and Friedman (16), and by McIlvain (17).

In the veratrole group, some experiments were conducted on the hydrolysis of 4,5-dinitroveratrole (I) by 40% hydrobromic acid, and the products isolated were the corresponding dinitroguaiacol (II) and dinitropyrocatechol (III). The former was identified by its m.p. (172–173°), the analysis of its scarlet sodium salt, and the conversion of this salt into 4,5-dinitroveratrole (I) by the action of methyl sulfate. The identity of the dinitropyrocatechol was established by its analysis, the analysis of its steel-blue disodium salt, and the methylation of the last named to the dinitroveratrole (I).

The 4,5-dinitropyrocatechol (III) was reduced to the diaminopyrocatechol (IV) by sodium hydrosulfite in aqueous solution. As Hoehn (18) has shown, the free (IV) oxidizes rapidly in the air to the diamino-*o*-quinone. No attempt was made, therefore, to isolate a pure (IV), but the reduction product of the dinitropyrocatechol was converted directly into the dihydroxyquinoxaline (VII) by condensation with glyoxal.

For the reduction of the 4,5-dinitroveratrole (I), the action of iron and hydrochloric acid upon its alcoholic solution was found more satisfactory than the use of tin and hydrochloric acid (1).

This diamine (VIII) was condensed with glyoxal to the corresponding quinoxaline (IX). The latter was very stable to nitrating agents. The product usually obtained was a mixture of the mononitro derivative (X) and of the corresponding guaiacol type (XI). No dinitro derivative was isolated in any of the experiments. Although no pure mononitro derivative was obtained, the product was sufficiently pure to yield the corresponding monoamino derivative on reduction. As this monoamine (XII) was identical with the monoamine which resulted when 3,4,5-triaminoveratrole was condensed with glyoxal, the nitro group in (X) must be in position 8, and the structure of the aminodimethoxyquinoxaline must be (XII).

To contribute to the solution of the engrossing problem of the dependence of physiological action upon chemical constitution, a sulfanilamido (XIII) and a *beta*-diethylaminoethyl derivative (XIII) of the 8-amino-6,7-dimethoxyquinoxaline were prepared and tested but, as noted beyond, neither showed any promise of therapeutic usefulness.

4,5-Dinitroguaiacol was similarly reduced to the diamine (V), and the latter condensed with glyoxal to the methoxyhydroxyquinoxaline (VI). This latter compound was also separated as one of the products in the attempted conversion of 8-amino-6,7-dimethoxyquinoxaline (XII) into the corresponding 8-hydroxy-6,7-dimethoxyquinoxaline by diazotization. In another series of experiments, 8-amino-6,7-dimethoxyquinoxaline was diazotized in the presence of fairly strong sulfuric acid and treated with potassium iodide. The product was an unidentified crystalline iodo derivative, decomposing around 210°, insoluble in boiling water, readily soluble in cold dilute sodium carbonate solution, and which formed methoxyhydroxyquinoxaline (VI) when treated with an aliphatic amine in *n*-butanol solution.

In another group of experiments, the aminodimethoxyquinoxaline was converted into the diazoacetate which was decomposed by heating withcopper powder, and on working up yielded the methoxyhydroxyquinoxaline (VI), and a crystalline product, m.p. 163–164°, which gave (VI) when digested with alkali.

ACKNOWLEDGMENTS

We are indebted to Merck & Co., Rahway, N. J., through the courtesy of Dr. Randolph T. Major, Research Director, for the pharmacological testing of our sulfanilamidoquinoxaline (XV); and to the Survey of Antimalarial Drugs for their screening tests on the 8-(*beta*-diethylaminoethylamino)-6,7-dimethoxyquinoxaline (XV), and also on the sulfanilamido derivative (XV).

EXPERIMENTAL

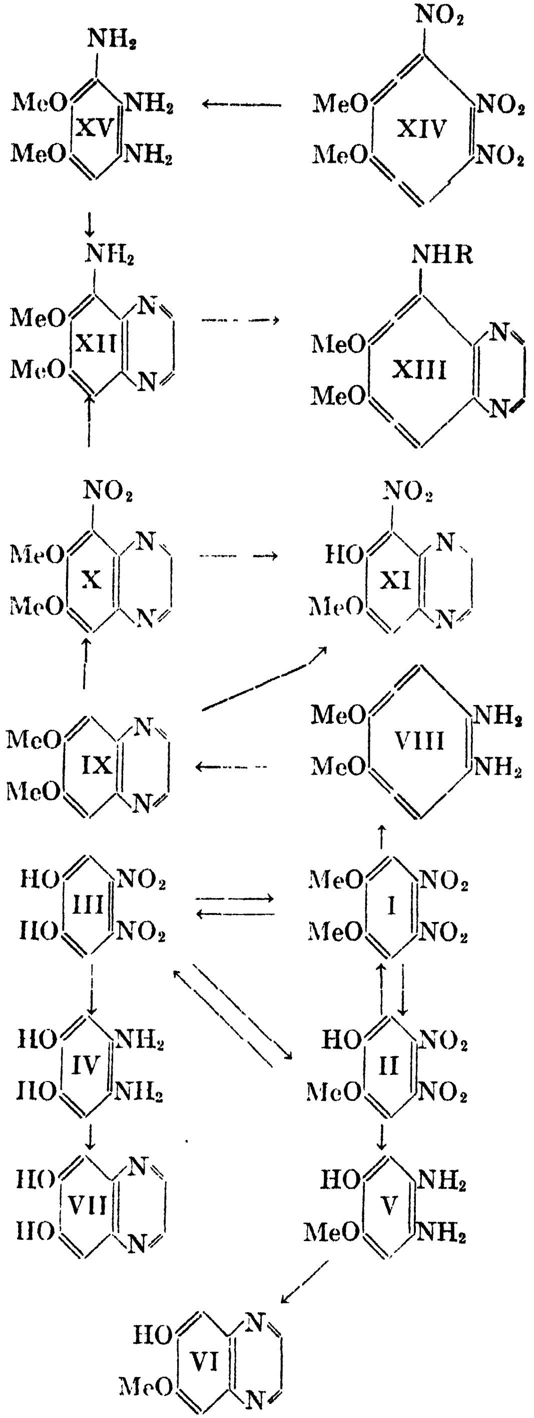
Unless otherwise specified, all m p.'s recorded have been corrected for thermometer stem exposure.

DMQx. In what follows, this stands for *dimethoxyquinoxaline*, and *Qx* for quinoxaline.

4,5-Dinitroveratrole (I). The following method of preparation is considered an improvement upon that described by Frisch and Bogert (1).

To 192 cc. of concentrated nitric acid (sp. gr. 1.42), at 0–3°, 69 g. of veratrole was added dropwise, with stirring, during at least 80 mins. After continuing this stirring for another 5 mins., the temperature was permitted to rise to 3–5°, 105 cc. of concentrated sulfuric acid run in slowly (1 hr.), and the mixture stirred for 15 mins. longer at the same temperature. The pale yellow crystalline mixture was warmed gradually (20 mins.) to 54–55°, kept there for 10 mins., and the temperature then raised (5 mins.) to 58–60° and held at that point for 10 mins. There resulted a thin canary slurry which, in 5 mins., was cooled to 23–25°, poured slowly into a mixture of 200 g. of ice and 200 cc. of water, and the mixture then diluted with water to a volume of 2500 cc. The product was a pale yellow liquid, with a deposit of yellow

Flow Sheet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NH₂
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XII
MeO
N
NHR
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sandy crystals. After occasional stirring for 30 mins., this was filtered, the solid washed repeatedly with water until the last wash was neutral, and dried at 50–52° for at least 16 hrs.: m.p. 126–127°; yield, 94–96%. Frisch and Bogert (1) found the m.p. 127–128° for their product.

Further purification by recrystallization from alcohol, in the presence of Norit SG Neutral and Dicalite Superaid, gave fine pale yellow needles, m.p. 130–131°.

The pure compound was difficultly soluble in water or *n*-heptane, cold or hot. In methanol, it was moderately soluble hot, but only slightly soluble cold. In cold benzene it was moderately soluble, but dissolved easily when the temperature was raised. Its solubility in 100 cc. of alcohol was approximately 0.8 g. at 23°, and 6 g. at 75°; in 100 cc. of *n* butanol, 1 g. at 23°, and 33 g. at 110°.

Action of hydrobromic acid upon 4,5-dinitroveratrole. When 5 g. of 4,5-dinitroveratrole was refluxed for 11 hours with 50 cc. of 40% hydrobromic acid, it yielded two alkali-soluble products, one of which (a) was freely soluble in water, while the other one (b) was not. The crude product (b) was converted into a solution of the sodium salt in order to eliminate a little insoluble unchanged dinitroveratrole. After reprecipitation with dilute hydrochloric acid and recrystallization from 50% ethanol, in the presence of active carbon and a filter-aid, it was obtained in pale yellow hair-like crystals, m.p. 172–173°, in agreement with the m.p. recorded in the literature (19) for *4,5-dinitroguaiacol*; yield, 1.15 g. Its identity was further established by analysis of its sodium salt, and remethylation of the latter to *dinitroveratrole* (m.p 130°).

Anal. Calc'd for $C_7H_5N_2NaO_6$· Na, 9.76. Found: Na, 9.88.

Dinitroguaiacol (II) was only slightly soluble in hot water or *n*-heptane, but quite soluble in alcohol or ether. It crystallized well from toluene or 50% alcohol, and was not volatile with steam.

Its scarlet sodium salt was salted out by excess of strong aqueous sodium hydroxide, sodium carbonate, or brine, and was but slightly soluble in absolute alcohol. The ammonium salt was more easily soluble, and was reprecipitated in orange crystals by 15 *N* ammonium hydroxide solution.

4,5-Dinitropyrocatechol (III) The 4,5-dinitropyrocatechol recovered by ether extraction from the hydrobromic acid filtrate and washings in the preparation of the dinitroguaiacol, after purification formed canary sandy crystals, melting with decomposition at 166.5–167.5°; yield, 1.12 g. A mixture of benzene and nitroethane proved to be the best medium for its crystallization. The product gave a positive nitrogen, but negative halogen and negative Liebermann nitroso test. It was soluble in water (to a yellow solution), ethanol, *n*-butanol, acetone, nitroethane, ether, or dichloroethyl ether; slightly soluble in boiling benzene, xylenes, heptane, or *o*-dichlorobenzene; fairly hygroscopic, not volatile with steam, and stable to hot dilute silver nitrate solution. Its aqueous solution was slightly acid to Congo and became purple when made alkaline. By acidification and extraction with ether, the (III) was recovered.

Anal of this product, still slightly impure, gave the following results:

Calc'd for $C_6H_4N_2O_6$: C, 36.0; H, 2.0

Found: C, 35.6; H, 1.93.

Attempted determination of nitrogen gave such erratic results as to be worthless.

The anhydrous disodium salt was quite soluble in 80% alcohol, but only slightly in absolute alcohol. It was prepared with absolute alcoholic sodium hydroxide and was isolated in dark steel-blue crystals, which exploded violently at elevated temperatures.

Anal. Calc'd for $C_6H_2N_2Na_2O_6$: Na, 18.75. Found: Na, 18.75, 18.95.

Under 6 cc. of dry toluene, 0.225 g. of the dry disodium salt was pulverized, 0.5 cc. of freshly distilled methyl sulfate added, and the mixture refluxed for 16 hours. After chilling, 3 cc. of water was added, followed by 3 cc. of 5 *N* ammonium hydroxide. The purpose of the latter was not only to destroy excess of the methyl sulfate, but also to retain in the aqueous layer any unchanged dinitropyrocatechol and intermediate dinitroguaiacol.

The flask was stoppered, well shaken, some Filter-Cel added, and the mixture filtered with suction through crepe paper into a small separatory funnel, flushing with a small quantity of toluene and dilute ammonium hydroxide. After 15 mins.' shaking the charge was allowed to stand for an hour, and separated into a pale yellow upper toluene layer and a lower blood-red aqueous one. The toluene layer was washed with a small amount of water, and acidification of these aqueous extracts yielded some *4,5-dinitroguaiacol* (m.p. 172–173°), as a fluffy yellow precipitate. From the toluene layer, *4,5-dinitroveratrole* was isolated (0.1 g.) which melted at 130° when crystallized from alcohol, and showed no change in this m.p. when mixed with an authentic sample of different origin.

4,5-Diaminopyrocatechol (IV) has been described by Hoehn (18), who obtained it by reducing 4-acetamino-5-nitrosopyrocatechol in alcoholic solution with stannous chloride, and found that the free base was very sensitive to the oxygen of the air, rapidly changing into the 4,5-diamino-*o*-quinone.

Attempts to reduce 4,5-dinitropyrocatechol, in aqueous solution with metallic iron or zinc; or, in alcoholic solution, by the action of hydrogen, in the presence of the Adams-Voorhees catalyst, yielded a very impure product.

Instead of trying to separate a pure diamine, however, it was found much more satisfactory to condense the reduction product of the dinitro coupound (III) directly with glyoxal, to the *6,7-DihydroxyQx* (*VII*), according to the following procedure: A solution of 14.5 g. of commercial 90% powdered sodium hydrosulfite in 80 cc. of water was chilled to 5°. To this, there was added rapidly a solution of 2 g. of 4,5-dinitropyrocatechol in 20 cc. of water, while the temperature was kept down by an ice-bath. After standing for 5 mins. longer at low temperature, the mixture was warmed gradually (5 mins.) to 65–67°, held there for 5 mins. (not much longer, or a red dye begins to form), and the clear yellow solution then chilled rapidly to 28–30° and 10 cc. of glacial acetic acid added.

Three g. of glyoxal bisulfite powder (Carbide and Carbon's $C_2H_2O_2 \cdot 2NaHSO_3 \cdot H_2O$, M.W. 284, glyoxal content 20%) was introduced in one lot, the mixture stirred for about 10 mins. at 28–30°, to aid solution, warmed (15 mins.) to 95–100°, and held at that temperature for an hour. After cooling to room temperature and standing for 2 hrs., the precipitate was filtered out, washed thoroughly with water and dried at 55° to constant weight; yield, 1.3 g., or 81%. Sublimed at 255° and 1 mm. pressure it was obtained as a yellow crystalline solid, which began to darken at 260° and finally charred without fusion. It was too sparingly soluble to be crystallized from any of the neutral solvents tried. It dissolved quite readily in dilute sodium carbonate or ammonium hydroxide to a clear yellow solution. Reprecipitated by dilute acetic acid, a very stable colloidal yellow suspension was formed, not coagulated by heating whereas acidification of the preheated solution reprecipitated the original compound in crystalline form. The sublimate was obviously a very weak base since, at room temperature, it was insoluble in and unchanged by N hydrochloric acid. With 3 N hydrochloric acid, it formed the violet crystalline *monohydrochloride*, which was only very slightly soluble (about 1% at 98°) in acid of this strength. Suspended in water, this salt was hydrolyzed to the insoluble yellow free base and the water became strongly acid to Congo paper.

The monohydrochloride, when dried for 2 hrs. at 56°, lost no weight.

Anal. Calc'd for $C_8H_6N_2O_2 \cdot HCl$: C, 48.4; H, 3.5; N, 14.1; Cl, 17.8.
Found: C, 48.1; H, 3.55; N, 14.1; Cl, 17.5.

4,5-Diaminoguaiacol (V) *and 6-Methoxy-7-hydroxyQx* (VI) *from 4,5-Dinitroguaiacol.* The dinitroguaiacol (2.14 g.) was reduced in alcoholic solution by iron and hydrochloric acid, and then condensed with glyoxal, essentially as described in the following for the preparation of the 6,7-DMQx (IX) from the diaminoveratrole.

The crude product was obtained in pale pinkish matted crystals, m.p. 236–237.5°; yield, 1.51 g. Recrystallized from 50% (by volume) ethanol, it formed silvery nacreous plates, m.p. 238–239°.

Anal. Calc'd for $C_9H_8N_2O_2$: C, 61.4; H, 4.55; N, 15.9.
Found: C, 60.72; H, 4.47; N, 15.85.

The *copper salt* was prepared by the addition of copper sulfate to an aqueous solution of the sodium salt. Warmed with 0.25 normal acetic acid, a clear solution was obtained, which deposited nacreous leaves of the initial compound (m.p. 238–239°) as it cooled. This copper salt dissolved readily in normal ammonium hydroxide solution at room temperature to a clear green solution, which precipitated copper sulfide with normal sodium sulfide, and with normal sodium hydroxide formed a blue cupric hydroxide jelly. Neither cupric nor lead acetates gave any precipitates with the initial compound in alcoholic solution.

The canary yellow *silver salt* was difficultly soluble even in warm dilute acetic acid. It was variable in composition, apparently indicating a changing proportion of neutral and basic salts.

This salt reacted readily with cold dilute sodium sulfide solution or warm dilute sodium hydroxide solution.

Neither the copper nor the silver salt gave any evidence of being a chelate compound.

Benzoyl derivative. Subjected to a Schotten-Baumann reaction with benzoyl chloride, this compound (VI) yielded pale tan nacreous leaves (from alcohol), m.p. 136.5–137.5°; soluble in ethanol, benzene, or hot heptane; difficultly soluble in water, or in cold heptane.

Anal. Calc'd for $C_{16}H_{12}N_2O_3$: C. 68.6; H, 4.3; N, 10.0.
Found: C. 68.64; H, 4.9; N, 10.02.

4,5-Diaminoveratrole (VIII) was prepared by Frisch and Bogert (1) by reducing the dinitro compound (I) with tin and hydrochloric acid. For the present investigation, we used iron and hydrochloric acid upon an alcoholic solution of the nitro compound, as described beyond in the case of the trinitroveratrole (XIV). Of the dinitro derivative, 11.4 g. was used; and of the trinitro, 9.1 g., the rest of the charge remaining practically the same in the two cases.

6,7-DMQx (IX). To the final solution of the reduction product from 11.4 g. of 4,5-dinitroveratrole (I), without attempting to separate the pure free base, and at a temperature of 28–30°, there was added all at once 15.6 g. (10% excess) of finely powdered glyoxal sodium bisulfite, and the mixture stirred to effect solution. In a closed flask, shaken occasionally (2 hrs.), this solution separated a pale fluffy crystalline precipitate of the quinoxaline sought (IX). After 20 hrs.' standing at 28–30° the precipitate was filtered out, washed thoroughly with water, and dried at 50° to constant weight (about 20 hrs.); yield, 7.2 g.; m.p. 149–150°. The combined aqueous filtrates were extracted with benzene, the extract concentrated to crystals, and the latter dried for four hrs. at 50°. There was thus obtained 1.1 g. of pale yellow crystals, m.p. 147–148°, making a total yield of 8.3 g. By recrystallization from water, the m.p. was raised to 149.5–150.5°.

For analysis, a sample recrystallized from water was crystallized from alcohol, decolorizing with active carbon, and yielded long white needles, m.p. 150–151°.

Anal. Calc'd for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7.
Found: C, 63.5; H, 5.4; N, 14.6.

In water, 100 cc. dissolved about 0.17 g. at 20°, and 2.1 g. at 95°; in alcohol, about 3.5 g. at 24°, and 12.5 g. at 60°; 100 cc. of glacial acetic acid dissolved about 5.0 g. at 25°, and 10 g. at 50°. It was moderately soluble in ether or benzene cold, quite soluble in hot benzene; very weakly basic, dissolving only in large excess of *N* hydrochloric acid; not volatile at 50° but, in thin layers at 100° lost about 0.6% per hour. Refluxed with 40% hydrobromic acid, a brown amorphous infusible material was obtained, insoluble in all solvents tried. With 30% hydrobromic acid, the original substance was recovered unaltered.

Nitration of 6,7-DMQx (IX). 6,7-DMQx was quite stable to concentrated nitric acid (sp. gr. 1.42) even at its b.p. Attacked by mixed acid, it was found impossible to obtain the mononitro derivative without some simultaneous hydrolysis of a methoxyl group; but no dinitro derivative was detected in any of the nitration experiments.

Eleven and four-tenths grams of (IX) was gradually fed to a mixture of 120 cc. of concentrated (95.5%) sulfuric acid + 30 cc. of concentrated nitric acid (sp. gr. 1.42), at 23–25°, during an hour, let stand for 40 hours longer at the same temperature and then poured into 240 g. of ice and 240 cc. of water. The mixture was diluted with ice-water to a volume of 900 cc., the orange precipitate removed, washed repeatedly with water, and as much as possible of the adhering water removed by suction. This crude product was a mixture of soda-soluble and soda-insoluble nitration products, the separation of which proved very difficult.

The still moist cake, containing about 10.3 g. of dry material, was added to 340 cc. of water at 23–25°, and 2 *N* aqueous sodium carbonate solution added in 2-cc. portions, until a five minute test with alkacid paper (pale green color) was obtained. Total soda used was about 22 cc. The solution became blood-red, with some yellow solid in suspension.

It was believed that the soda-soluble substance was probably the *6-methoxy-7-hydroxy-8-nitroquinoxaline* (XI) because of the red color of its alkaline solution, its acidity to Congo, the fact that an alkoxyl group *ortho* to a nitro group is more readily hydrolyzed than when in the *meta* position, and by a preliminary determination of sodium in the sodium salt. The soda-insoluble constituent should then be the simple *8-nitro-6,7-DMQx* (X).

The soda-insoluble material was collected by extraction with benzene at 40–42°, the filtered benzene extract concentrated to crystals, and the latter dried at 50° to constant weight. The product was a pale brown crystalline cake; yield, 5.6 g. (39.7% of that calculated for a m.w. of 235). This was crystallized twice from alcohol in the presence of a decolorizing carbon, and then formed colorless hair-like needles, m.p. 122–124°.

Analysis of various samples of this product showed that it was not the pure 8-nitro-6,7-DMQx (X) expected although, as noted beyond, the 8-amino compound (XII) was obtained from it by direct reduction.

It was only slightly soluble in ether or boiling water; fairly soluble in hot cyclohexanol or glacial acetic acid; quite soluble in cold benzene, dioxane, or nitroethane. Its solubility in 100 cc. of ethanol at 23° was about 0.9 g.; at 75°, 4 g.; in 100 cc. of benzene at 23°, about 8.3 g. It was not volatile at 50°, or with steam. In a thin layer at 100°, it lost about 0.1% hourly. Suspended in boiling 3 *N* sodium hydroxide it was slowly hydrolyzed to the following compound.

6-Methoxy-7-hydroxy-8-nitroquinoxaline (XI). The original aqueous solution of the soda-soluble product from which the soda-insoluble substances had been removed by filtration and benzene extraction, was made strongly acid to Congo with 3 *N* hydrochloric acid, the pale yellow precipitate removed, washed thoroughly with water, and dried at 50–52°; yield, 3 g. (22.2% of that calculated for m.w. of 221). This crude material was purified by reconversion into its sodium salt with sodium carbonate and decolorization of the hot clear red aqueous solution of the latter. As it cooled, the solution separated the sodium salt in bright orange needles, which were removed, washed with acetone, and air-dried to constant weight. Further drying at 100° showed a loss of only 1.2%. From an aqueous solution of this purified sodium salt, the free hydroxy compound was precipitated with 3 *N* hydrochloric acid, washed with water, and dried to constant weight at 50°.

Anal. Calc'd for $C_9H_7N_3O_4$: C, 48.47; H, 3.17; N, 19.0.
Found: C, 48.48; H, 3.26; N, 18.92.

The compound appeared in pale yellow crystals, which began to darken at 235° and then charred without melting. Heated slowly on a porcelain dish, it suddenly flared without previous melting. In hot solvents, it was difficultly soluble in water, ether, ethanol, benzene, or nitroethane; and only slightly soluble in glacial acetic acid, dioxane, or cyclohexanol. Although the aqueous solution contains only a small amount of the compound, it was fairly acid to Congo. It gave a negative test for sulfur, and was not volatile with steam, or at 50°, but in a thin layer at 100° lost about 0.1% hourly. At 23°, a solution of 1 g. in 2.5 cc. of 2 *N* sodium carbonate and 65 cc. of water, is about saturated; at 95°, the same result was secured with 10 cc. of water. Reduction of this compound was not attempted, because of lack of material.

Analysis of the purified sodium salt showed 9.72% sodium; calc'd for $C_9H_6N_3NaO_4$, 9.47% Na.

This sodium salt was very resistant to alkylation, and experiments conducted with methyl iodide, methyl sulfate, or methyl *p*-toluenesulfonate, failed to yield any 8-nitro-

6,7-DMQx. The same was the case with the free hydroxy compound in pyridine solution. Diazomethane was not tried.

8-Amino-6,7-DMQx (XII). To a mixture of 13.8 g. of finely divided iron in 83 cc. of water was added 2.8 cc. of 2 *N* acetic acid. The mixture was warmed to 93-95°, and 5.5 g. of the crude nitro compound (X) was fed in gradually (30-35 mins.). After 10 mins. further stirring at 93-95°, 83 cc. of hot water was added, then (5 mins. later) 5.5 cc. of 2 *N* sodium carbonate solution, and finally 0.6 g. of active carbon, bringing the temperature finally to 98°. The mixture was filtered, the clear pink filtrate cooled to about 25°, seeded with a few crystals of (XII) prepared from 3,4,5-triaminoveratrole (XV) (see beyond), and left for 20 hours in the refrigerator. The separated garnet crystals were collected, washed with cold water, and dried for 6 hours at 50°; yield, 1.7 g.; m.p. 101-103°.

This crude product was dissolved to a clear red solution in 100 cc. of benzene. A single extraction of this solution with 13 cc. of *N* hydrochloric acid, and treating this extract with about 1 g. of powdered sodium carbonate yielded 0.9 g. of a brown crystalline material, m.p. 101-103°. The residual clear yellow benzene solution was washed with dilute sodium carbonate solution and concentrated to pale orange crystals, m.p. 106-107.5°; yield, 0.7 g. Further purification was effected by crystallization from water, decolorization with active carbon, and a final crystallization from isopropanol, giving coarse bright yellow needles, m.p. 107.5-108.5°. Mixed with an equal weight of (XII) prepared from (XV), the m.p. was 107-108°.

Anal. Calc'd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.37; N, 20.49.

Found: C, 58.80, 58.69; H, 5.50, 5.22; N, 19.86, 20.98.

3,4,5-Trinitroveratrole (XIV), prepared by adding veratrole to a mixture of concentrated nitric acid and concentrated sulfuric acid, essentially as described by Frisch and Bogert (1), was purified by crystallization from benzene, in the presence of a decolorizing carbon and a suitable filter-aid, instead of using alcohol as the solvent. The purified product melted at 144.5-145.5°, in agreement with the literature (20, 21). It was difficultly soluble in water, heptane, or methanol, cold or hot; only slightly soluble in toluene or *n*-butanol cold, easily soluble hot. In 100 cc. of alcohol, its solubility was approximately 0.4 g. at 19°, 4 g. at 75°; in 100 cc. of benzene, 3.3 g. at 18°, 33.3 g. at 80°.

3,4,5-Triaminoveratrole (XV). The reduction of the trinitro derivative (XIV) was conducted in a 2-liter 3-necked round-bottom Corning flask, carrying a thermometer (with bulb in the mixture) in one side opening, and a rubber stopper in the other, with the central opening available for a reflux condenser.

There was first placed in the flask 33.5 g. (0.6 atom) of steel card teeth (No. 33 W & M gage wire) This excess (200%) of iron was found necessary for complete reduction There was then added 190 cc. of U.S.P. alcohol and 105 cc. of concentrated hydrochloric acid (sufficient to convert the base into its trihydrochloride and all iron into ferrous chloride). The temperature of the mixture rose to about 41° and there was some evolution of gas. To the mixture, 1.4 cc. of 10 *N* stannous chloride solution was run in, and a minute later 9.1 g. (0.033 mole) of trinitroveratrole. After warming carefully on the water-bath so that the reflux temperature (85-86° in the mixture) was reached in about 17 mins., and continuing this refluxing for an hour longer, the charge was cooled to 70°, the flask removed and 500 cc. of water added A Hopkins bulb was fitted in the central opening, connected with a descending condenser and exactly 570 cc. distilled off (90 mins.). The temperature of the mixture rose gradually from the initial b.p. of 87°, to about 106°. The distillate contained all of the original alcohol and some hydrochloric acid. Some metallic iron was still present in the flask. The mixture was cooled to 65°, the flask removed, stoppered loosely, cooled to 25°, and decanted through a small bare Büchner funnel into a 750-cc. Erlenmeyer flask. The residual iron was rinsed with two 25-cc. portions of water and the washings added to the main filtrate, giving a total volume of about 245 cc. To prevent air oxidation of the base during subsequent partial neutralization, 8 g. of anhydrous sodium sulfite powder was dusted in, and dissolved quite rapidly with little heat effect. The solution, still decidedly acid to Congo, and at a temperature of 25-30°, was treated with small portions of

2 *N* aqueous sodium carbonate. Foam was collapsed by addition of a few drops of ether. The last 5 cc., at the end-point gave no foam, but a small precipitate of ferrous carbonate persisted, and the solution was acid to litmus, but neutral to Congo; total sodium carbonate solution required was about 132 cc. Most of the ferrous chloride remained in solution at this point.

One g. of filter-aid and 1 g. of active carbon were added, the whole mixed for 5 mins. at 25–30°, and filtered with suction. The filtrate was pale apple-green and quite sensitive to air oxidation. The best yields of the glyoxal condensation product were secured from this liquor, by carrying out the reaction in the suction flask.

To isolate the crude base, after the addition of 8 g. of sodium sulfite, the solution was diluted to 400 cc., and powdered sodium carbonate added at 25–30° until all of the iron was precipitated and Brilliant Yellow paper showed an alkaline reaction (red). The solution was heated to 70–75° and rechecked for alkalinity, adding more carbonate if necessary. A filter paper spot test with aqueous sodium sulfide showed no iron present. After 10 minutes' heating at 70–75°, a little filter-aid was dropped in, and the mixture filtered with suction. The material on the filter was washed with four 50-cc. portions of hot water, the combined filtrates bleached with a little sodium hydrosulfite, and extracted with chloroform in a continuous extraction apparatus and in an inert gas. The yield of base was 85%, m.p. 146-150°. [Literature (1), 150–152°.] It was easily soluble in water, aniline or hot alcohol; only slightly soluble in cold alcohol, hot benzene, or hot chloroform; difficultly soluble in ether.

Condensation of 3,4,5-triaminoveratrole with glyoxal. As noted in the description of the reduction of the trinitroveratrole (XIV), the best yields of the quinoxaline (XII) were obtained by using the final reduction liquor in the suction flask.

To that liquor, at 25–30°, 10.4 g. (10% excess) of finely powdered glyoxal sodium bisulfite was added, and the mixture stirred for 15 minutes. The flask was then stoppered, shaken occasionally during 2 hrs., and left for 20 hrs. at 25–30°. A crop of brilliant canary crystals separated. Without removing these crystals, the mixture was extracted with benzene, and the solvent removed from this extract. The residue, dried for 2 hrs. at 50°, formed a pale brown crystalline mass, m.p. 106–107°; yield, 4.25 g. Recrystallized from water, in the presence of active carbon, it formed yellow crystals, m.p. 106.5–107.5°; yield, 3.4 g. From the filtrates and mother liquors, an additional 0.2 g. was recovered of the same m.p. As noted in the foregoing, a 50:50 mixture of this compound with the 8-amino-6,7-DMQx (XII) prepared by direct reduction of 8-nitro-6,7-DMQx (X), showed the m.p. 107–108°.

One hundred cc. of water dissolved about 0.4 g. at 22°, and 3.6 g. at 90°. It was moderately soluble in ether or alcohol, and quite soluble in benzene; difficultly soluble in dilute acetic acid, sodium carbonate, hydroxide, or bisulfite. In dilute hydrochloric acid, it dissolved to a clear ruby solution, from which the bright yellow original substance was reprecipitated by alkali. About 0.3 g. per liter was carried over in the steam distillate.

Anal. Calc'd for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.3; N, 20.5; M.W., 205.

Found: C, 59.2; H, 5.1; N, 20.5; M.W. (by titration with 0.1 *N* sodium nitrite), 205.

8-(N^4-Acetylsulfanilamido)-6,7-DMQx (XIII). To a well stirred solution of 12 g. of powdered 8-amino-6,7-DMQx (XII) in 75 cc. of dry pyridine, was added gradually (20 mins.) 18 g. or 1.32 times the calculated quantity of freshly prepared and finely powdered acetylsulfanilyl chloride, maintaining the temperature of the mixture at 25–28° during the addition and for 15 minutes after the addition was completed. After it had been heated for an hour at 100°, it was cooled to about 23°, the flask closed and left for 15 hrs. at laboratory temperature. It was then poured into an excess of cold water, chilled, stirred, allowed to settle, and the crystalline solid filtered out, washed thoroughly with water, and dried for 10 hrs. at 50–55°; yield, 18.2 g.; m.p. about 234–235° (with decomposition).

To the combined mother liquors was added 51 cc. of 3 *N* aqueous sodium acetate solution, and the mixture was distilled with steam until 1600 cc. of distillate was collected. The liquid remaining in the distilling flask was concentrated to 120 cc., filtered hot, the insoluble crystalline cake washed with hot water, and dried for four hours at 50–55°. There was thus recovered an additional 4.4 g. of the product sought (XIII), making a total of 22.6 g., or 98% of that calculated.

For analysis, 1 g. of this crude product was digested with 25 cc. of 50% acetic acid, 0.1 g. of filter-aid, and 0.1 g. of active carbon, for 30 minutes at 100°, the mixture filtered hot, the filter paper washed with a little hot acetic acid, the pale salmon filtrate allowed to cool to 25°, then left in the refrigerator overnight. The crystalline precipitate was washed once with 4 cc. of 50% acetic acid, followed by three 4-cc. portions of water, and the pale yellow crystals dried for 5 hrs. at 50–55°. These crystals melted at 238.5–239°, with sudden decomposition. A repetition of this purification process failed to alter the m.p.

Anal. Calc'd for $C_{18}H_{18}N_4O_5S$: C, 53.73; H, 4.48.
Found: C, 53.87; H, 4.78.

The crude product (m.p. 234–235°) was difficultly soluble in water, isopropanol, or toluene, when hot; and slightly soluble in hot *n*-butanol. In boiling ethanol, about 1.4 g. dissolved in 100 cc., and 0.3 g. at 21°. In 100 cc. of 50% acetic acid, 0.8 g. dissolved at 21°, and about 5 g. at 100°. It was difficultly soluble in cold 3 *N* hydrochloric acid, and dissolved in hot 3 *N* sodium hydroxide with hydrolysis.

8-Sulfanilamido-6,7-DMQx (XIII). The above acetyl derivative was hydrolyzed by digestion at 100° with 3 *N* hydrochloric acid. After cooling, the product was precipitated with aqueous sodium carbonate, filtered out, and washed with water. The crude product was decolorized and crystallized from alcohol and further purified by crystallization from 1-nitropropane. It then formed pale yellow prisms, m.p. 217.5–218.5°, with some decomposition; and was readily soluble in dilute sodium hydroxide.

Anal. Calc'd for $C_{16}H_{16}N_4O_4S$: C, 53.33; H, 4.44.
Found: C, 53.64; H, 4.82.

Pharmacological tests were carried out on this compound in the Merck & Co. laboratories, and it was found to have practically no bacteriostatic or bactericidal properties. It was also subjected to screening tests by the Survey of Antimalarial Drugs (SN 9162), and found to be without promise as an antimalarial.

8-(beta-Diethylaminoethylamino)-6,7-DMQx (XIII). Great difficulty was experienced in attempting to replace a hydrogen of the 8-amino group by a dialkylaminoalkyl group, irrespective of the method employed. Either no reaction at all occurred, or the products were resinous.

Attempts were made to react the amine (XII) with *beta*-diethylaminoethylchloride, in the presence of various condensing agents, including phenol (22), and pinene (23). *beta*-Diethylaminoethylpyridinium benzenesulfonate was also tried, and likewise the condensation with 1-diethylamino-4-pentanone, followed by reduction of the resultant azomethine. Some measure of success, however, was achieved in the following experiment.

A mixture of 7.5 g. of (XII) with 75 cc. of fused phenol formed a bright orange solution when warmed on a steam-bath. In this hot solution, there was dissolved 9.4 g. of *beta*-diethylaminoethyl chloride hydrochloride. After heating the liquid for 7 hrs. at 100°, it was cooled to 20–25° and 6.75 g. of Eastman "Sodium Phenoxide Anhydrous" fed in. Warmed to complete solution and heated at 100° for 17 hrs., it was then cooled to 20–25°, diluted with 75 cc. of water, acidified with 16 cc. of 3 *N* hydrochloric acid and most of the phenol blown out with steam. The mixture remaining in the flask was cooled to 20–25°, filtered, 3 *N* sodium hydroxide added to strong alkaline reaction, and the mixture extracted with benzene. The benzene extract was shaken first with anhydrous sodium sulfate, then with active carbon, and finally with Filter-cel and filtered. After elimination of the solvent, the pressure was reduced and, on redistillation at 1 mm. pressure, two fractions were collected: (a) thin, pale yellow oil, b.p. about 130°, 1.2 g.; (b) viscous orange oil, b.p. about 205°, 5.7 g. (51.3% yield). For analytical samples, these fractions were redistilled at 1 mm., taking the middle cuts to ampoule receivers.

Fraction (*a*). Slightly soluble in cold water, to alkaline reaction, still less soluble in hot, halogen-free, volatile with steam; soluble in dilute hydrochloric acid, and with difficulty in dilute sodium hydroxide.

Anal. Calc'd for $C_{12}H_{19}NO$: C, 74.61; H, 9.84.
Found: C, 73.5; H, 10.4.

It is suggested that this product may be an impure ether of the following constitution: $Et_2N(CH_2)_2OPh$ (24, 25). Such compounds have been prepared by Levy and Ditz (25) and others, and were found to diminish, suppress, or reverse the pharmacodynamic action of adrenaline.

Fraction (*b*). Very slightly soluble in cold water to alkaline reaction, insoluble in hot, halogen-free, not volatile with steam; easily soluble in many of the usual neutral organic solvents, difficultly soluble in dilute sodium hydroxide. Soluble in dilute hydrochloric acid to a deep cherry solution; b.p. 175° at 0.5 mm. Attempts to form crystalline salts with inorganic or organic acids, by wet or dry methods, gave only hygroscopic gummy products.

Anal. Calc'd for $C_{16}H_{24}N_4O_2$: C, 63.16; H, 7.89; N, 18.42.
Found: C, 62.92; H, 7.70; N, 17.45, 17.63.

Through the courtesy of the Survey of Antimalarial Drugs, a sample of this product (SN 12,366) was examined pharmacologically and found to be practically devoid of any appreciable antimalarial effect.

Attempts to carry out this same phenol-phenate process, using $MeCHBr(CH_2)_3NEt_2$, or the corresponding chloride instead of $Cl(CH_2)_2NEt_2$, proved futile.

Production of 6-methoxy-7-hydroxyQx (VI) *from 8-amino-6,7-DMQx* (XII). A solution of 2.05 g. of (XII) in 30 cc. of water and 3 cc. of 13.5 *N* sulfuric acid, was diazotized with sodium nitrite at 0–5°. A slight excess of nitrous acid was destroyed by the addition of 0.1 g. of sulfamic acid, 27.5 cc. of 8.5 *N* sodium hydroxide added with cooling, and the mixture heated at 100°. Some suspended crystalline material, presumably a diazotate, began to dissolve at about 85° and evolution of gas occurred. After 90 minutes at 100°, the mixture was cooled to 20–25°, filtered, and the small amount (0.09 g.) of residue washed with water. To the filtrate and washings, amounting to a total of 77 cc., there was added 23 cc. of 9 *N* acetic acid, and the strongly acid mixture was digested at 100° for about 20 minutes, then cooled to 20°, the precipitate removed, washed with water and dried for 4 hrs. at 50–55°, giving a pale pink cake; yield, 0.91 g. Crystallized twice from 50% (by vol.) ethanol, there was obtained 0.74 g. of silvery nacreous flakes, m.p. 238–239°, apparently identical with the compound (VI) obtained from 4,5-diaminoguaiacol and glyoxal

Subjected to a Kjeldahl analysis, with precipitated copper powder as digestion catalyst, it showed N 15.3% (calculated for a hydroxymethoxyquinoxaline, 15.9).

Diazotization reactions applied to 8-amino-6,7-DMQx. All attempts to obtain the corresponding 8-hydroxy, or 8-halogen-6,7-DMQx, from the 8-amino compound (XII), by the usual Sandmeyer or Gattermann reactions, were unsuccessful, but some of the observations made in the course of the experiments were interesting, especially when the decomposition of the diazonium compound was catalyzed by the use of moderately strong sulfuric acid, as in the following experiment.

(a) *Production of an iodo derivative.* To a clear red solution of 5 g. of the aminoDMQx (XII) in 147 cc. of 48.1% sulfuric acid, at 0–3°, finely powdered sodium nitrite (about 1.8 g.) was added gradually. Excess of free nitrous acid was destroyed by the addition of about 0.24 g. of sulfamic acid, and 5.3 g. of powdered potassium iodide was dropped in (as one lot), keeping the temperature at 0–3° and maintaining the stirring. With evolution of nitrogen, a brick-red precipitate separated and, after an hour, the temperature was raised to 23° and left at that point for 20 hours. After dilution with 366 cc. of water, a little sodium bisulfite solution was poured in to remove any free iodine, and the mixture was filtered. The precipitate was washed with small lots of water, until the washings gave a practically negative test with Congo, and was then dried at 55–57° to constant weight. This crude product formed a pinkish cake; yield, 6.55 g. It was decolorized and recrystallized from nitroethane, yielding nacreous pale yellow fine leaves, which decomposed around 210° without melting and, on analysis, gave figures which did not agree satisfactorily with those calculated for a monoiodo derivative of either 6-methoxy-7-hydroxy-, or 6,7-dimethoxy-Qx.

Found: C, 41.55; H, 3.0; I, 40.0; N, 10.43. Calc'd for $C_9H_7IN_2O_2$: C, 35.8; H, 2.3; I, 42.1; N, 9.3. Calc'd for $C_{10}H_9IN_2O_2$: C, 38.0; H, 2.9; I, 40.2; N, 8.9. The iodine was determined according to the Raney nickel-aluminum method of Schwenk, Papa, and Ginsberg (26).

Although quite insoluble in boiling water, it dissolved quite rapidly in cold dilute sodium carbonate solution, and then gave a strong test for iodide ion, thus suggesting the presence of a free hydroxyl group and an unusually mobile halogen. Acidification of this alkaline solution yielded an amorphous precipitate, which was insufficient for further investigation.

When some of this crystalline iodine compound was added to a solution of 1-diethylamino-4-aminopentane in *n*-butanol, and the crude product crystallized from 50% ethanol, silvery nacreous plates were obtained, melting at 238–239° to a dark red liquid, which gave a positive test for nitrogen, but a negative one for halogen. The yield from 3.2 g. of initial iodine compound was 1.2 g., and of purified product 1.0 g. It was difficulty soluble in hot water, ether, or *n*-hexane; fairly soluble in hot toluene or ethanol. In boiling 50% (by volume) ethanol, 100 cc. dissolved 2.9 g., and 0.2 g. at 4°. It was only slightly soluble in dilute acetic acid, but dissolved in 3 *N* hydrochloric acid or in cold 2 *N* sodium carbonate solution. Its solubilities, m.p., and other properties identified it as *6-methoxy-7-hydroxyQx* (VI), as produced from 4,5-diaminoguaiacol and glyoxal.

(b) *Decomposition of a diazoacetate.* 8-Amino-6,7-DMQx was diazotized in the usual way and normal sodium acetate solution was added. After the introduction of a small quantity of copper powder (in the absence of copper, this diazoacetate was unchanged by refluxing), the mixture was heated for an hour at 100°, nearly neutralized by anhydrous sodium carbonate, heated for 5 minutes, and filtered hot. By working up the precipitate and the solids separated from the filtrates and washings, an 11.9% yield of 6-methoxy-7-hydroxyQx (VI) was isolated, m.p. 238–239°.

From the mother liquors, there was recovered a compound, m.p. 161–162°, which was crystallized from a 1:1 mixture of benzene and *n*-heptane and decolorized. It then formed pale orange sandy crystals, m.p. 163–164°, difficultly soluble in hot water or boiling ether, fairly soluble in hot *n*-heptane; more easily soluble in ethanol, *n*-butanol, chloroform, ethyl acetate, or benzene, when hot. Its analysis showed C, 54.51; H, 3 20; N, 24.44.

By the action of hot 2 *N* sodium carbonate solution, or 3 *N* sodium hydroxide, it yielded 6-methoxy-7-hydroxyQx (VI), m p. 238–239°.

The results of the experiments in which a methoxyhydroxyQx was formed from an initial dimethoxyQx indicate that one of the two methoxyl groups in the latter is very easily hydrolyzed.

SUMMARY

1. 4,5-Dinitroveratrol can be hydrolyzed by hydrobromic acid to a mixture of 4,5-dinitroguaiacol and 4,5-dinitropyrocatechol, both of which can be reconverted into the initial dinitroveratrole by methyl sulfate.

2. 4,5-Diamino derivatives of pyrocatechol, guaiacol or veratrole condense readily with glyoxal to the corresponding quinoxalines.

3. 3,4,5-Triaminoveratrole condenses with glyoxal to the 8-amino-6,7-dimethoxyquinoxaline and not to the 5-amino-7, 8-dimethoxy isomer.

4. From the 8-amino-6,7-dimethoxyquinoxaline, a sulfanilamido, and a *beta*-diethylaminoethyl derivative, were prepared and subjected to pharmacological tests by Merck & Co., and by the Survey of Antimalarial Drugs. The sulfanilamido derivative proved to be without appreciable antimalarial, bacteriostatic, or bactericidal properties, and the diethylaminoethyl derivative was practically devoid of antimalarial effect.

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[From the Research Laboratories of Hoffmann-La Roche, Inc.]

ACYCLIC ENEDIOLS. A NEW METHOD OF PREPARATION

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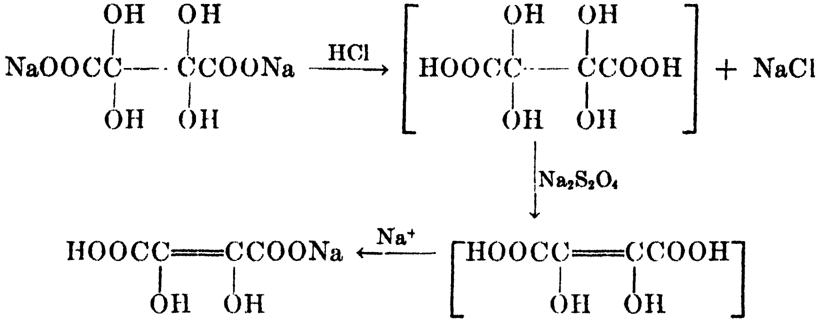
During the course of an investigation of anti-oxidants in these laboratories, it was decided to prepare some acyclic enediols upon the supposition that such compounds would exhibit pronounced activity as anti-oxidants. A search through the literature revealed that information pertinent to the enediol structure was very meager, and that few enediols had ever been synthesized. In fact, of the acyclic enediols, only dihydroxymaleic acid and its dimethyl and diethyl esters were known (1). In addition, a sample of the dilauryl ester of dihydroxymaleic acid was obtained through the courtesy of Dr. A. Weissberger of Eastman Kodak Company. Quite surprisingly, the dilauryl compound, though analyzing correctly, did not exhibit the anticipated reducing action upon iodine.

Dihydroxymaleic acid was first prepared by Fenton (2) who described its reactions and elucidated its structure in a series of papers (3, 4, 5, 6, 7). The method first used by Fenton (2) involved the oxidation of tartaric acid with hydrogen peroxide in the presence of a little iron as catalyst. This method, and a slight modification by Nef (8), constituted the standard procedure for making the enediol. It is significant that Fenton and other workers in this field (9), with but one exception, failed to report the yields obtained in this reaction, which would seem to indicate that the yields were poor. Fischer and Feldman (10), using a modification of Nef's procedure, reported a notable yield of 24% of discolored product. In these laboratories an attempt to reproduce the work of Fischer and Feldman resulted in a 3.5% yield of crude dihydroxymaleic acid.

To obviate the need of preparing the enediol esters from the difficultly prepared and relatively unstable dihydroxymaleic acid, it was decided to esterify before incorporating the enediol structure into the molecule. Accordingly, disodium dihydroxytartrate was esterified with ethyl alcohol as described by Anschütz and Parlato (11). The resulting ester was then subjected to reduction. H_2S proved an immediate failure, so recourse was had to hydrogenation with Raney nickel and platinum as catalysts. The desired diethyl dihydroxymaleate could not be isolated despite repeated attempts under a variety of conditions. The reaction products however gave a strong enol test with ferric ion and pyridine and had some reducing action on iodine, which proved on analysis to be approximately 1.5% of theory.

At this rather discouraging stage of the investigation, an attempt was made to use sodium hydrosulfite as the reducing agent. The result obtained with this reagent was gratifying. The reduction went rapidly—within the space of a few minutes—and produced an almost pure product in good yield. The reaction was subsequently tried with the methyl, *n*-propyl, *n*-butyl, and *n*-amyl esters of diketosuccinic acid and in all cases, the corresponding enediol esters were readily obtained. The esters all gave the characteristic enol test with ferric ion and pyridine and reduced the theoretical quantity of iodine in acid solution. It was interesting to note, however, that the higher esters were slower in reducing iodine than the lower esters. This phenomenon might account for the failure of Weissberger's dilauryl ester to react with iodine at all.

In addition to the esters, the monosodium salt of dihydroxymaleic acid was also readily prepared by this process. To obtain this salt, disodium dihydroxytartrate was converted to the corresponding acid by means of HCl, and the acid was reduced to the enediol with sodium hydrosulfite. Instead of the free dihydroxymaleic acid however, the relatively insoluble monosodium salt precipitated out. The reaction may be represented schematically as follows:



$$NaOOC\overset{OH}{\underset{OH}{C}}-\overset{OH}{\underset{OH}{C}}COONa \xrightarrow{HCl} \left[HOOC\overset{OH}{\underset{OH}{C}}-\overset{OH}{\underset{OH}{C}}COOH\right] + NaCl$$

$$\left[HOOC\overset{OH}{\underset{OH}{C}}-\overset{OH}{\underset{OH}{C}}COOH\right] \xrightarrow{Na_2S_2O_4} \left[HOOC\underset{OH}{C}=\underset{OH}{C}COOH\right]$$

$$HOOC\underset{OH}{C}=\underset{OH}{C}COONa \xleftarrow{Na^+} \left[HOOC\underset{OH}{C}=\underset{OH}{C}COOH\right]$$

The monosodium dihydroxymaleate was in turn esterified with methyl alcohol and hydrogen chloride. The resulting dimethyl dihydroxymaleate was identical in all respects with the compound previously prepared by reduction of dimethyl diketosuccinate.

The diketosuccinic esters prepared in this study were obtained as oils which ranged in color from yellow to orange, due to the presence of the chromophoric alpha diketo group. Upon solution of the oils in water or alcohol it was noted that the color was immediately discharged, a change ascribable to destruction of the chromophoric grouping by hydration or alcoholation. Thus, dimethyl diketosuccinate which was obtained as a yellow-orange oil, readily hydrated even on exposure to atmospheric moisture, to form a white crystalline dihydrate which melted at 110–112°.

The isomeric picture presented by the enediols is rather complicated. Theoretically, several geometric and optical isomers are possible for each compound. For example, diethyl dihydroxymaleate may exist in both ketonic and enolic form. Moreover, in the ketonic form two optically active isomers and a racemate are possible whereas the enolic variety presents the possibilities of cis-trans isomerism.

Fenton (1, 2) succeeded in isolating two isomeric forms of the dimethyl and diethyl dihydroxymaleates. The dimethyl ester (2) was obtained in two forms which had the same melting point, but differed in crystal structure and solubility. The diethyl ester (1), melting initially at 72–73° was resolved into two components, one of which (α form) melted at 68°, and the other (β form) at 126–128°. The two forms varied considerably in chemical properties. The α variety was readily acetylated with acetyl chloride to give the diacetoxy derivative, whereas the β form did not react even on prolonged boiling. Treatment with acetic anhydride, however, converted the β ester to the α form. The α variety also decolorized permanganate instantly whereas the β compound reacted rather slowly.

An interesting observation made by Fenton and confirmed by the present study was that diethyl dihydroxymaleate, though stable in air, was rapidly oxidized and dehydrated when kept in air over a desiccant. Fenton (1) later reported that this remarkable instability was a characteristic of the α form; the β form was completely stable. In general, Fenton found the α form to be the more reactive isomer but was unable to determine conclusively whether the difference in properties was due to keto-enol tautomerism or cis-trans isomerism. He was however inclined to favor the former interpretation.

In this study, no attempt was made to separate the isomeric forms of the esters. However, in the light of Fenton's findings, and in view of the fact that the butyl and amyl esters react much more slowly with iodine than the lower esters, it may be postulated that the esters of dihydroxymaleic acid, when synthesized as described above, are obtained as mixtures of α and β forms and that the proportion of the less reactive β form increases with increasing molecular weight.

Acknowledgment. The author wishes to acknowledge his gratitude towards Dr. H. M. Wuest for his many suggestions and encouragement during the course of this work.

The author is also indebted to Dr. A. Steyermark for the microanalyses.

EXPERIMENTAL

All melting points are corrected.

Diketosuccinic esters. The esters listed in Table I were all prepared according to the method of Anschütz and Parlato (11). To illustrate the general procedure, the preparation of diamyl diketosuccinate is described in detail.

A suspension of 120 g. of disodium dihydroxytartrate in 480 cc. of normal amyl alcohol was saturated with hydrogen chloride at 0°. The mixture was permitted to stand in the refrigerator for 3 days, and was filtered to remove the precipitated sodium chloride. The clear filtrate was distilled under vacuum (water-pump) and the amyl alcohol was removed to yield a yellow oily residue. Upon distillation of the yellow oil, 55 g. of an orange-yellow fraction was obtained boiling at 120–127° at 0.4–0.5 mm.

Anal. Calc'd for $C_{14}H_{22}O_6$: C, 58.7; H, 7.7.
Found: C, 59.1; H, 8.0.

Dimethyl dihydroxymaleate. This compound was prepared by two methods:

(a) Ten grams of dimethyl diketosuccinate (dihydrate) dissolved in a few cc. of water was added to a cold solution of 10 g. of sodium hydrosulfite in about 65 cc. of water. A white crystalline precipitate appeared almost immediately and was filtered off to give 9 g. of nearly pure product melting at 148–152°. Fenton and Wilks (1) reported the melting point 151°. However, upon recrystallization from benzene the enediol ester was obtained in the form of colorless needles and plates melting at 174–175° and soluble in hot and insol. in cold benzene, alcohol, and water. The product gave a deep blue color with dilute ferric chloride solution and 1 drop of pyridine.

Anal. Calc'd for $C_6H_8O_6$: C, 41.0; H, 4.6; Mol. wt., 176.
Found: C, 40.7; H, 4.6; Mol. wt. (iodine titration), 176.5.

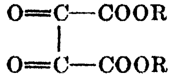
(b) Twenty grams of disodium dihydroxytartrate was dissolved in 5 *N* hydrochloric acid. To the solution was added a large excess of acetone and the precipitated sodium chloride was filtered off. The acetone was then removed under vacuum, and a solution of 15 g. of sodium hydrosulfite in water was added to the residue. A heavy white crystalline precipitate of monosodium dihydroxymaleic acid appeared upon scratching the walls of the vessel; yield 11 g.

The monosodium salt (9 g.) dissolved in methyl alcohol was saturated at 0° with hydrogen chloride and the mixture was permitted to stand at room temperature overnight. The methyl alcohol and water were removed under vacuum at low temperature, and the residue was dissolved in hot benzene, filtered to remove the sodium chloride, and cooled. Two grams of dimethyl dihydroxymaleate was obtained, which was identical with the product obtained in (a).

Diethyl dihydroxymaleate. Diethyl diketosuccinate (2.5 g.) was treated with an excess of sodium hydrosulfite in cold aqueous solution. A precipitate of fine white needles appeared immediately. The needles gave the characteristic enediol test with ferric ion and pyridine. On reprecipitation from methyl alcohol with water, the needles melted at 71–73° (5); yield 1 g.

TABLE I

DIKETOSUCCINIC ESTERS



$$\begin{array}{l} O{=}C{-}COOR \\ \quad\;\, | \\ O{=}C{-}COOR \end{array}$$

R=	APPEARANCE	B.P.°C/MM.	n_D^{25}	ANALYSIS Calc'd C	ANALYSIS Calc'd H	ANALYSIS Found C	ANALYSIS Found H
Methyl[a]	Yellow-orange oil	102–110/12–13	—	34.3	4.8	34.8	4.8
Ethyl[b]	Yellow oil	108–113/8–10	1.4420	—	—	—	—
n-Propyl[c]	Orange oil	100–108/1–2	1.4307	50.1	6.3	49.7	6.9
n-Butyl	Orange oil	125–130/0.8–1	1.4325	55.8	7.0	56.3	7.1
n-Amyl	Orange-yellow oil	120–127/0.4–0.5	1.4368	58.7	7.7	59.1	8.0

[a] Analyzed as dihydrate, $C_6H_6O_6+2H_2O$, white crystals, m.p. 110–112°.

[b] Reported in the literature, b.p. 115–117° at 12 mm., n_D^{20} 1.4341, 1.4280.

[c] Analyzed as hemihydrate, $C_{10}H_{14}O_6+0.5\ H_2O$.

Di-n-propyl dihydroxymaleate. To a suspension of 10 g. of the corresponding diketone in 20 cc. of cold water was added a cold solution of 10 g. of sodium hydrosulfite in 100 cc. of water. The suspended oil solidified after a short while. The reaction mixture was then strongly cooled, and the product was filtered off and washed with ice-water; m.p. 67–69°. On recrystallization from warm methyl alcohol (40°), the enediol ester was obtained in the form of colorless plates melting at 68–70°; yield 4.5 g of pure material.

Anal. Calc'd for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9; Mol. wt., 232.

Found: C, 51.4; H, 7.0; Mol. wt. (iodine titration), 240.

Di-n-butyl dihydroxymaleate. Ten grams of the corresponding diketone in 20 cc. of cold water was added to a solution of 10 g. of sodium hydrosulfite in 20 cc. of cold water. The reaction mixture was stirred at room temperature for about 15 minutes or until precipitation was complete and then was strongly cooled. The precipitate was filtered off and washed with ice-water to yield 9 g. of nearly pure product. The enediol ester was further purified by solution in methyl alcohol at room temperature and then adding water to incipient cloudiness. Upon cooling to −10° with occasional stirring, colorless plates were obtained which melted at 34°; yield 7.8 g. of pure material.

Anal. Calc'd for $C_{12}H_{20}O_6 + 0.5CH_3OH$: C, 54.4; H, 8.0.
Found: C, 54.4; H, 8.0.

Di-n-amyl dihydroxymaleate. The diketone (9.5 g.) was treated with sodium hydrosulfite as described for the dibutyl compound. The product was obtained in the form of glistening colorless plates melting at 29-30°; yield 5.2 g.

Anal. Calc'd for $C_{14}H_{24}O_6 + CH_3OH$: C, 56.3; H, 8.8.
Found: C, 56.3; H, 8.3.

SUMMARY

A new method has been elaborated for the preparation of enediols of the dihydroxymaleic ester type. The process involves the reduction of diketosuccinic esters to the corresponding enediols with sodium hydrosulfite. The reductions are rapidly effected and result in good yields of almost pure products. The enediols thus formed all reduce iodine, but the rate of reduction decreases with increasing molecular weight.

NUTLEY, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

CERTAIN 1-NAPHTHYL KETONES[1]

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In the past, preparation of 1-naphthyl ketones has presented a number of difficulties. The single most important method for their synthesis has been the Friedel-Crafts reaction.

In 1886, Pampel and Schmidt (1) prepared methyl 1-naphthyl ketone by the reaction of naphthalene in petroleum ether with acetyl chloride in the presence of anhydrous aluminum chloride. Later in this same year, Claus and Feist (2) used carbon disulfide as the diluent in another preparation of this ketone. Then Rousset (3) found that the addition of an equivalent amount of the acyl chloride in small portions to a boiling carbon disulfide solution of naphthalene and aluminum chloride gave a mixture of 1- and 2-naphthyl ketones. He prepared thus the following 1- and 2-naphthyl alkyl isomers: methyl, ethyl, *n*-propyl, isopropyl, and isobutyl. Separation of the pairs of isomers was effected by conversion into picrates and recrystallization of the latter; this procedure is long and laborious and seldom gives wholly satisfactory results.

Stobbe and Lenzer (4) published in 1911 a somewhat improved method for the preparation of methyl 1- and 2-naphthyl ketones through initial formation of an aluminum chloride complex with acetyl chloride in carbon disulfide and interaction with naphthalene below 15°. About this time Caille (5) described a procedure whereby freshly sublimed aluminum chloride was added in small portions to a carbon disulfide solution of naphthalene and acyl chloride cooled to 0°. He claimed high yields of ketones requiring only a single crystallization (or distillation) to produce pure alkyl 1-naphthyl ketones, specifically, methyl, ethyl, *n*-propyl, and isopropyl. However, more recently Samuelsson (6) has stated that regardless of the temperature of reaction, when using this procedure in no case is the pure alkyl 1-naphthyl ketone obtained. And Fieser (7) has pointed out that through Caille's procedure a small amount of 2-naphthyl ketone is formed, but does not appear in the final product because the complex is soluble in the carbon disulfide used.

By alkylation of methyl 1-naphthyl ketone, through treatment with the theoretical quantity of sodamide and subsequent addition of the appropriate alkyl halide, the ethyl, *t*-butyl, and *t*-amyl ketones have been prepared by Volmar (8). He, too, found that it was necessary to form and recrystallize the picrates to secure separation from the starting material.

1-Naphthyl phenyl ketone and di-1-naphthyl ketone have been prepared by means of the Grignard reaction. Thus in 1913, Tschitschibabin (9) allowed

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1-naphthylmagnesium bromide to react with 1-naphthonitrile. The reaction product was hydrolyzed with ammonium chloride to give the ketimine which, in turn, was decomposed by boiling with sulfuric acid. Grignard (10) prepared both ketones by action of 1-naphthylmagnesium bromide on cyanogen chloride, to give the nitrile, and subsequent addition of a second equivalent of the arylmagnesium halide. In each case the product was hydrolyzed by chipped ice yielding the ketimine which was separated as the hydrochloride; this salt was decomposed by boiling in water. Wilmart (11) modified Grignard's method by the addition of cyanogen chloride to the Grignard reagent, to form the nitrile, and by isolation of the ketimine as the sulfate.

TABLE I

1-NAPHTHYL KETONES, $C_{10}H_7COR$

—R	YIELD, %	B.P., °C/MM.	B.P., °C/MM.	d^{20}_4	n^{20}_D	MOLEC. REFRACT.		C		H	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
Methyl	52	148–150/8[a]		1.1203[a]	1.6257[b]	53.59	53.76				
Ethyl	37	169–170/11[c]		1 0971[e]	1.6108[d]	58.21	55.51				
n-Propyl	63	178–179/12		1.0722[e]	1.5988[f]	62.83	62.83				
Isopropyl....	39	159/20[g]		1.0666	1.5948	62.83	62.66				
n-Butyl .	46	184–186/10	331–333/745	1.0562	1.5894	67.45	67.45	84.86	84.93	7.60	7.75
Isobutyl	48	178–180/10[h]		1.0500[h]	1.5848[i]	67.45	67.42				
n-Amyl.....	44	199–201/12	346–348/744	1.0394	1.5808	72.16	72.22	84.91	84.62	8.02	8.11
Isoamyl ..	51	183–185/8	339–341/745	1.0395	1.5795	72.16	72.08	84.91	84.48	8.02	8.12
n-Hexyl... ..	35	196–198/7	355–357/745	1.0251	1.5728	76.78	76.91	84.95	84.86	8.39	8.34
Cyclohexyl...	37	206–208/8	[j]					85.67	85.20	7.61	7.71
Phenyl	55		74.5–75.5[k]								

[a] Rousset, ref. 3, reported b.p. 154–156°/5 mm.; d^0_0 1.1336.

[b] Caille, ref. 7, recorded n^{27}_D 1.622.

[c] Rousset reported b.p. 166–168°/8 mm., d^0_0 1.1082.

[d] Caille recorded n^{27}_D 1.606.

[e] Rousset reported d^0_0 1.0861.

[f] Caille recorded n^{27}_D 1.596.

[g] Rousset reported b.p. 172–174°/8 mm.; d^0_0 1.0761.

[h] Rousset reported b.p. 180–182°/9 mm.; d^0_0 1.059.

[i] Caille recorded n^{27}_D 1.582.

[j] M.p. 62.5–63.5°.

[k] Fieser, "Experiments in Organic Chemistry," Heath, New York, 1935, p 193, reported m.p. 76°.

In this study, the Grignard reaction involving 1-naphthonitrile has been found to be entirely satisfactory for the synthesis of eleven 1-naphthyl ketones, five of which have not previously been reported. Since bromine reacts readily with naphthalene to form 1-bromonaphthalene, which subsequently may be converted smoothly into 1-naphthonitrile (12), the structure of the ketones, prepared from the latter by means of the Grignard reaction, is unambiguous.

EXPERIMENTAL

Preparation of alkyl l-naphthyl ketones. A typical preparation was as follows: to a Grignard reagent prepared from magnesium turnings (0.21 gram atom) and an alkyl bromide (0.22 mole) in 250 ml. of anhydrous ether, 1-naphthonitrile (0.20 mole) in 300 ml. of anydrous toluene was added over a period of one hour with continuous stirring. The ether was removed by distillation and the toluene solution was refluxed for five hours. After cooling, the ketimine was obtained by hydrolysis of the toluene solution with 100 ml. of saturated ammonium chloride and chipped ice. The aqueous layer was then separated from the toluene solution and extracted once with ether. The ether and toluene extracts were combined and extracted twice with 100-ml. portions of dilute sulfuric acid. These two acid extracts were combined, extracted once with ether, and heated at reflux temperature for two hours, cooled, and extracted twice with an ether-benzene mixture. The ether-benzene extracts were washed with water, twice with saturated sodium carbonate solution, and twice with saturated sodium chloride solution. The ether-benzene layer was then concentrated and distilled under diminished pressure.

In some of the preparations, a modification of the foregoing procedure was used in that the toluene solution of the nitrile was added to the Grignard reagent in boiling ether. This variation was found to give equally good results and shortened the time interval required for distillation of the ether.

It was found also that in some cases when the removal of ether was incomplete, considerably lower yields were obtained. This point was quite clearly illustrated in the synthesis of *n*-amyl 1-naphthyl ketone. Of the latter, two preparations, using the same molar quantities and essentially the same procedure, were made. In the first experiment, it was evident that the ether had been incompletely removed and a yield of only 11% was obtained; in the second experiment, care was taken to remove the ether completely and a yield of 44% was realized.

Certain physical and analytical data for the eleven 1-naphthyl ketones are listed in Table I.

SUMMARY

By means of the Grignard reaction, involving pure 1-naphthonitrile and appropriate Grignard reagents, eleven 1-naphthyl ketones have been prepared; this represents the initial synthesis of five of these ketones.

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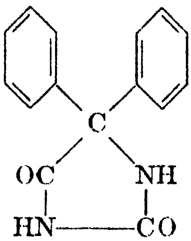
[Contribution from the Department of Chemistry, The University of Texas]

CERTAIN 5-(1-NAPHTHYL)-5-SUBSTITUTED HYDANTOINS[1]

HENRY R. HENZE and LESLIE GREY NUNN, Jr.[2]

Received February 25, 1947

Attempts have been made in this and other laboratories to produce satisfactory anticonvulsants by synthesis of derivatives of diphenylhydantoin (A) through introduction of substituents into one or both of the phenyl groups. To date, such alterations have yielded only less active compounds. However, some 5-phenyl-5-substituted hydantoins have been prepared, chiefly in this Laboratory, and have been shown elsewhere (1) to possess a desirable degree of anticonvulsant activity. Likewise, anticonvulsant activity has been demonstrated in a few spirohydantoins whose structural formulas may be written to emphasize a close relationship to 5-phenylhydantoin, namely: fluorenone-spirohydantoin (B), (2), α-hydrindone-spirohydantoin (C), (3), and α-tetralone-spirohydantoin (D), (3).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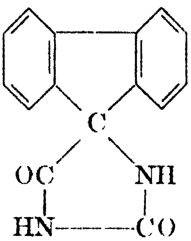
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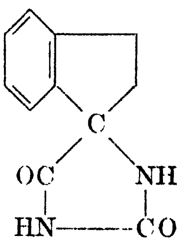
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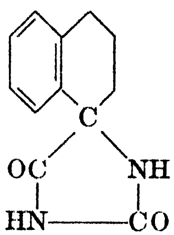
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The structural relationship of the napththyl groups to the phenyl group is well known, indeed the former may be thought of as being disubstituted phenyl groups (*i.e.*, phenylene radicals); or else the 1-naphthyl group (E) may be looked upon as being simultaneously a benzyl group (F) and a phenylbutadienyl radical (G). Likewise, the 2-naphthyl group (H) may be considered as being both a styryl group (J) and a cinnamyl radical (K). The pharmacological activity of these four groupings (F, G, J and K) when attached to the hydantoin nucleus has scarcely been investigated; however, the benzyl group, in certain alkaloids of the papaverine type and in simple esters, has been shown by Macht (4) to have a tendency to relax unstriated muscles. It seemed, therefore, of considerable interest to attempt to synthesize a series of 5-naphthylhydantoins; and the 1-naphthyl series was selected as being the more likely to possess useful pharmacological activity.

In this investigation the series of 1-naphthyl ketones recently synthesized (5) was converted into 5,5-disubstituted hydantoins through utilization of the

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[1] From the Ph. D. dissertation of L. G. Nunn, Jr., June, 1943.

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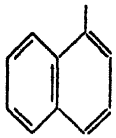

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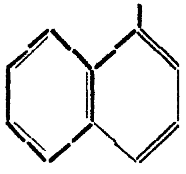

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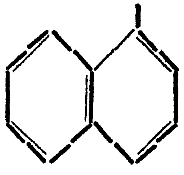

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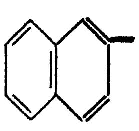

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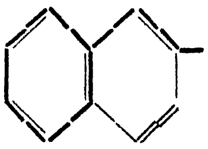

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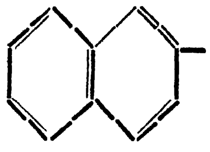

K

procedure developed in this Laboratory (6). In this manner, eleven 1-naphthyl ketones, separately dissolved in fused acetamide, reacted with ammonium carbonate and potassium cyanide to form the corresponding 5-(1-naphthyl)-5-substituted hydantoins.

A survey of the chemical literature revealed a previous report of a single conversion of a 1-naphthyl ketone into a hydantoin (7). This preparation involved, in sequence, the conversion of ethyl 1-naphthyl ketone into α-amino-α-(1-naphthyl)butyronitrile, the formation of α-ethyl-α-(1-naphthyl)hydantonitrile and, finally, production of the corresponding 5-ethyl-5-naphthylhydantoin for which the melting point 222–223° (cor.) was reported. The ethyl naphthyl ketone utilized in this synthesis was prepared by means of a Friedel-Crafts reaction following Caille's method (8); however, attention has been drawn (9) to the fact that this method does not always yield a pure product.

In this study, an authentic sample of ethyl 1-naphthyl ketone was converted into 5-ethyl-5-(1-naphthyl)hydantoin; the latter was found to melt at 186° (cor.). In hope of clarifying the discrepancy in melting points reported in these two investigations, a sample of purified 2-naphthonitrile[3] was allowed to react with ethylmagnesium bromide to form ethyl 2-naphthyl ketone;[4] the latter was converted into 5-ethyl-5-(2-naphthyl)hydantoin for which the melting point 222–223° (cor.) was noted.

EXPERIMENTAL

Preparation of 5-naphthyl-5-substituted hydantoins. The general method of preparation was as follows: Using a 1000-ml. Pyrex liner as a container, 0.05 mole of 1-naphthyl ketone was dissolved in 200 g. of fused acetamide (6). Nine grams of potassium cyanide was added and the mixture was stirred until all of the cyanide had dissolved; this precaution was found to be essential in order to avoid formation of an appreciable quantity of black tar during the course of the reaction. After placing the Pyrex container in a Monel metal bomb,

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[3] An Eastman Kodak Company product, m.p. 60–62°.

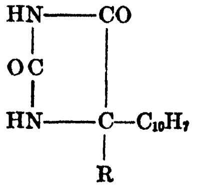
[4] Our sample of ethyl 2-naphthyl ketone melted at 56–57° (cor.), and its oxime melted at 132–133° (cor.); Rousset (9) reported this ketone and its oxime as melting at 56–57° (cor.) and 133° (cor.), respectively.

28.8 g. of ammonium carbonate (U.S.P. cubes) was added and the bomb was quickly closed to avoid loss of carbon dioxide and/or of ammonia. The bomb was placed in an oven regulated at 110° and heated for twenty-five hours.

The bomb was cooled to room temperature before being opened. A reddish-brown semisolid was obtained which was suspended in approximately 700 ml. of water and cautiously acidified with hydrochloric acid. The light brown, somewhat gummy material was filtered off and washed with water before being treated with 200 ml. of 10% sodium hydroxide solution. Unreacted ketone was removed by ether extraction, and the crude material was reprecipitated from the alkaline solution with hydrochloric acid. The solid was digested with 500 ml. of boiling ethyl alcohol and the solution filtered to remove a small amount of insoluble material. The alcoholic filtrate was diluted with 150 ml. of concentrated hydrochloric acid and warmed just below the boiling point for thirty minutes. After concentration of the solution to a volume of 150 ml., 400 ml. of water was added to ensure complete precipitation of the crude hydantoin. After filtration, and drying at 110°, the products were recrystallized from 50% methyl alcohol and from 50% dioxane solution or from both diluted solvents.

TABLE I

5-(1-NAPHTHYL)-5-R-HYDANTOINS



R	M.P., °C.(COR.)	YIELD,%	CARBON, % Calc'd	CARBON, % Found	HYDROGEN, % Calc'd	HYDROGEN, % Found	NITROGEN, % Calc'd	NITROGEN, % Found
$—CH_3$	217.5	54.0	69.99	69.85	5.04	5.29	11.66	11.58
$—CH_2CH_3$	186[a]	64.0	70.85	70.78	5.55	5.69	11.02	11.19
$—CH_2CH_2CH_3$	168–169	86.0	71.62	71.53	6.01	5.99	10.44	10.35
$—CH(CH_3)_2$	273–274	59.0	71.62	71.46	6.01	6.19	10.44	10.65
$—CH_2CH_2CH_2CH_3$	234–235	60.0	72.32	72.22	6.43	6.57	9.92	9.95
$—CH_2CH(CH_3)_2$	200–201	67.0	72.32	71.98	6.43	6.45	9.92	10.02
$—CHC_2H_5CH_2CH_2CH_3$	183.5–184.5	66.0	72.95	72.67	6.80	6.87	9.45	9.43
$—CH_2CH_2CH(CH_3)_2$	233–234	83.0	72.95	72.93	6.80	7.00	9.45	9.37
$—CH_2CH_2CH_2CH_2CH_2CH_3$	166–167	69.0	73.54	73.22	7.15	7.19	9.03	8.89
$—C_6H_{11}$(cyclo)	270–271	73.0	74.17	73.78	6.55	6.67	9.11	9.07
$—C_6H_5$	300–301	79.0	75.48	75.55	4.67	4.92	9.27	9.30

[a] Keach [*J. Am. Chem. Soc.*, **55**, 2979 (1933)] reported m.p. 222–23°, but that product is now believed to be the 2-naphthyl isomer.

Data concerning analyses and certain physical properties of these hydantoins appear in Table I.

Preparation of 5-ethyl-5-(2-naphthyl)hydantoin. Four and five-tenths grams (0.0246 mole) of ethyl 2-naphthyl ketone[3,4] was dissolved in 100 g. of fused acetamide. After 4.5 g. (0.069 mole) of potassium cyanide had been dissolved in this solution, 14.4 g. of ammonium carbonate was added and the reaction mixture was heated in the glass-lined Monel metal bomb at 110° for twenty-four hours. The product was purified in the same way as the isomeric 1-naphthyl hydantoins; after two recrystallizations from 50% methyl alcohol, 2.5 g. (38% yield) of light, white solid, melting at 222–223°, was obtained.

Anal. Calc'd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.12.
Found: C, 70.65; H, 5.66; N, 11.12.

SUMMARY

1. Eleven 1-naphthyl ketones, five of which are new, have been converted into the corresponding 5-(1-naphthyl)-5-substituted hydantoins.

2. 5-(2-Naphthyl)-5-ethylhydantoin has been synthesized and shown to be identical in melting point with the hydantoin previously reported as being 5-(1-naphthyl)-5-ethylhydantoin.

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[INSTITUTE OF TEXTILE TECHNOLOGY

REMOVAL OF ACETIC ACID AS A VARIABLE IN THE PERKIN REACTION

WILLIAM P. UTERMOHLEN, JR. AND E. LOUISE WALLACE

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In the standard procedure for the Perkin synthesis of cinnamic acids, recently reviewed by Johnson (1), a mixture of an aromatic aldehyde, an aliphatic acid anhydride (usually acetic anhydride), and an alkaline catalyst (sodium or potassium acetate, potassium carbonate, triethylamine, etc.) is heated under an air condenser. When acetic anhydride is used, the by-product of the synthesis is acetic acid, which is removed to some extent by evaporation through the condenser.

Johnson and his students, or earlier workers, have made studies of most of the possible experimental variables in this synthesis. One of these, addition of free acetic acid to the reaction mixture, was studied by Kalnin (2); his work showed that the addition of progressively larger quantities of glacial acetic acid effected successive decreases in yield of cinnamic acid, with either sodium or potassium acetate as catalyst. From this, it would seem that continuous removal of all of the acetic acid from the reaction mixture might lead to improved yields. Of course, low-boiling by-products have often been removed in other reactions (esterifications, ester exchange reactions, etc.) in order to force the reactions more nearly to completion. Accordingly, it was thought desirable to conduct some Perkin syntheses in which all of the acetic acid is removed as it is formed, in place of the usual conditions under which there is a partial, uncontrolled removal of the acid through an air condenser.

In order to do this, a distillation set-up was assembled which permitted applying sufficient heat to the reaction mixture, so that the acetic acid by-product and the unchanged acetic anhydride were forced off. These were separated in a heated distilling column with a total-condensation still head, the acetic acid being removed at a take-off and the acetic anhydride returned to the reaction mixture. The distilling column was of the Vigreux type, and was electrically heated by an external wrapping of Nichrome wire, heating being controlled by a variable rheostat. The reaction flask and column were so heated that there was a steady reflux at the top of the column; whenever the vapor temperature at this location was near the boiling point of acetic acid, a stopcock in the still head was opened and the condensate removed. This procedure will be called the "heated-column" method in this paper to distinguish it from the standard or "air-condenser" method usually employed.

This variation in the usual experimental procedure was studied for syntheses catalyzed by three different materials, sodium acetate, potassium carbonate, and potassium acetate.

Several runs were made using the standard method and molal quantities recommended by Johnson (1). The results served both as a check on technique, since they could be compared to those obtained by other workers using this method, and also as a means of evaluating yield results obtained with the heated-column method.

EXPERIMENTAL

Sodium acetate as a catalyst. A mixture of benzaldehyde (0.4 mole), acetic anhydride (0.6 mole), and fused sodium acetate (0.24 mole) was refluxed in an oil-bath at 170–175° for 8 hours, using an air-cooled condenser. The reaction mixture was then steam distilled to remove unreacted benzaldehyde. After the residual mixture was filtered, acidified, and cooled, the cinnamic acid precipitated. The crystals were filtered, washed, and dried to a constant weight. The conversion of benzaldehyde into cinnamic acid was 34%; and the yield, considering that about 0.17 mole of benzaldehyde was recovered, was about 60%. The standard method was reported in Johnson's review to give about 40% yields (corresponding to the quantities termed "conversions" in this work).

Reactions similar to the above were then carried out with the heated-column method. The temperature of the oil-bath was maintained at 180–190° and all liquid distilling between 117° and 125° was removed. (Acetic acid boils at 118.1°; acetic anhydride at 139.6°.) The total reaction times, molal quantities of reactants, and results are shown in Table I.

TABLE I

CINNAMIC ACID PRODUCED WHEN SODIUM ACETATE WAS USED AS A CATALYST

RUN	MOLES USED			REACTION		CONVERSION	YIELD
	Aldehyde	Anhydride	Catalyst	Method[a]	Time		
					hrs.	*per cent*	*per cent*
1	0.4	0.6	0.24	A	8	34	60
2	.4	.6	.24	B	10	46	62
14	.4	.6	.24	B	9	50	62
7	.4	.6	.24	B	24	61	72
5	.4	.6	.4	B	10	28	38
6	.4	.8	.4	B	7	46	63
3	.4	.6	.24[b]	B	7	33	52

[a] Method A = air-cooled condenser; B = heated column.

[b] Eight drops of pyridine added.

TABLE II

CINNAMIC ACID PRODUCED WHEN POTASSIUM CARBONATE WAS USED AS A CATALYST, HEATED-COLUMN METHOD

RUN	MOLES USED			REACTION TIME	CONVERSION YIELD	
	Aldehyde	Anhydride	Catalyst			
				hrs.	*per cent*	*per cent*
18	0.4	0.6	0.24	4S4[a]	51	67
8	.4	.6	.24	24	58	58[b]
9	.4	.6	.24	8	54	54[b]
10	.4	.72	.12	8	59	59[b]

[a] 4S4 = Reacted 4 hrs., stood overnight, reacted 4 hrs.

[b] Styrene formed and recovered rather than benzaldehyde.

Potassium carbonate as catalyst. When potassium carbonate was used as a catalyst in the heated-column method, the conversions of cinnamic acid were slightly better than those obtained with sodium acetate, but were only about the same as the yields reported in the literature for reactions run for similar lengths of time by the standard method with potassium carbonate. A summary of runs in which this catalyst was used appears in Table II.

Potassium acetate as a catalyst. The standard method was applied with potassium acetate as catalyst, using both the fused and the nonfused salt. Both conversion and yield values were appreciably higher with the fused catalyst, and only the latter material was used for subsequent runs with the heated-column procedure. The results of these experiments are shown in Table III.

TABLE III

CINNAMIC ACID PRODUCED WHEN POTASSIUM ACETATE WAS USED AS A CATALYST

RUN	MOLES USED			REACTION		CONVERSION	YIELD
	Aldehyde	Anhydride	Catalyst[a]	Method	Time		
					hrs.	*per cent*	*per cent*
11	0.4	0.6	0.24	A[b]	5	36	36[d]
12	.4	.6	.24	A	5	56	63[e]
13	.4	.6	.24	B[c]	4	59	59[d]
16	.4	.6	.24	B	8	58	80
17	.4	.6	.24	B	4S4[g]	57	57[f]

[a] Fused potassium acetate used in all but Run 11.

[b] A = air condenser used.

[c] B = Heated-column.

[d] Styrene formed.

[e] Styrene and benzaldehyde formed.

[f] No benzaldehyde or styrene obtained from reacted mixture.

[g] 4S4 = Reacted 4 hours, stood overnight with no heat, reacted 4 hours.

DISCUSSION

The heated-column method with sodium acetate catalyst gave higher conversions and about equal yields, compared to results obtained from the standard method (runs 2 and 14 *vs.* run 1). The addition of more catalyst gave poorer results (run 5) unless more anhydride was also present (run 6). The higher conversion and yield in run 7, compared to runs 2 and 14, were due to the longer time of heating, an observation frequently made by previous workers. One earlier investigator (3) claimed that a small amount of pyridine enhanced the yield materially. Neither this work (run 3) nor that by Johnson's group (1), substantiated this claim.

As was expected, syntheses catalyzed with potassium carbonate gave somewhat higher conversions (51–59%) than did runs of equal duration using sodium acetate. However, the material volatile with steam from these runs was frequently found to be styrene, or styrene mixed with a little benzaldehyde. In these cases a zero recovery of benzaldehyde was assumed, and hence, the yield was set equal to the conversion. Perhaps due to decarboxylation of part of the cinnamic acid already formed, the conversion and yield of acid were not increased by a long time of heating (run 8 *versus* runs 9 and 18). A change of proportions of anhydride and catalyst produced a slightly better conversion and yield (run 10 *versus* run 9). The standard method, using this catalyst, gave a 59% conversion for 8 hours reaction time, according to Johnson's review.

For syntheses catalyzed with fused potassium acetate, the standard method gave a conversion which was equal to that reported in Johnson's laboratory procedure, using the same reactants and conditions. Conversions were slightly higher when the heated-column method was used; the yields were erratic since benzaldehyde was not recovered regularly.

SUMMARY

Continuous removal by distillation of the acetic acid formed in the Perkin reaction enhanced the conversion, but not the yield, of cinnamic acid over those obtained by application of the standard method (in which no controlled removal of acetic acid is made) when sodium acetate was the catalyst, but did not significantly improve either conversion or yield when potassium carbonate or potassium acetate was the catalyst.

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[CONTRIBUTION FROM AUCKLAND UNIVERSITY COLLEGE]

THE ESSENTIAL OIL OF DACRYDIUM KIRKII

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A number of essential oils of the genus *Dacrydium* have already been examined, including *D. biforme*, "pink pine" (1), *D. colensoi*, "silver pine" (2), *D. cupressinum*, "rimu" or "red pine" (3), endemic to New Zealand, *D. franklinii*, "Huon pine" (4), occurring in Tasmania, and the wood-oil of *D. elatum* (5) from the Malay States, Borneo, the Phillippine and Fiji Islands. The diterpene phyllocladene is a constituent of all the oils with the exception of that of *D. elatum* and has already been recorded (6) in the leaf-oil of *D. kirkii*, a forest tree restricted to the lowland area between the Hokianga and Manukau harbors of the North Island of New Zealand.

A complete examination of the essential oil has now been made. The presence of 14 constituents has been shown, 8 of which have been identified, including a new sesquiterpene alcohol. Oils obtained in September and November had little variation in their respective constants, *viz.* yield, 0.086% (7–8 days after collection), 0.133% (4 days after collection); d_4^{25} 0.8798, 0.8768; n_D^{25} 1.4754, 1.4751; $[\alpha]_D^{25}$ +38.53°, +37.30°, acid number, negligible in both cases; saponification number, 7.6, 7.35; saponification number after acetylation, 21.3, 27.6; aldehydes, ketones, and phenols were absent.

Using a 90-cm. column of 27 theoretical plates after the pattern of Bower and Cooke (7), the oil was fractionated, the first portion at 10 mm., the middle fraction at 5 mm., and the remainder in a modified column at 0.01 mm., plotting the boiling point, refractive index, density, and optical rotation as the distillation proceeded. These results are summarized in Tables I and II. Only those fractions were examined whose physical constants indicated reasonable homogeneity.

Fractions 1–4 consisted of *d*-α-pinene whose constants are in agreement with those of specially purified α-pinene (8), confirmed by oxidation to *d*-pinonic acid with permanganate.

A minimum in the density curve indicated the presence of an acyclic terpene in fractions 10 and 11 and the presence of myrcene was established by the formation of its adduct with maleic anhydride, formed in 86% yield from fraction 10.

The highest rotation recorded for *d*-α-pinene is $[\alpha]_D^{20}$ +51.14°, obtained by Thurber and Thielke (9) by regeneration from its optically active nitrosochloride. Fraction 2 exceeds this and is the highest recorded for naturally occurring pinene. The small fraction 6 intermediate between pinene and myrcene, would indicate the presence of another compound of similar boiling point but of higher rotation. The obvious possibility is camphene but attempts to characterize it as camphenic acid resulted only in the isolation of pinonic acid.

The high rotations of fractions 15 and 16 indicated the presence of limonene, confirmed by the preparation of its tetrabromide.

TABLE I

FRACTIONATION OF *Dacrydium kirkii* OIL

FRACTION NO.	B.P. °C 10 MM.	n_D^{25} 1ST DROP	n_D^{25}	$[\alpha]_D^*$	d_4^{25}	WEIGHT, G.	CUMULATIVE %
1	38	1.4628	1.4629	+50.03	0.8538	105.48	26.7
2	38	1.4629	1.4637	+51.53	.8542	97.74	51.5
3	38	1.4638	1.4638	+53.0	.8538	8.49	53.6
4	38	1.4638	1.4637	+52.9	.8541	8.15	55.7
5	38.5–39	1.4639	1.4639	+53.4	.8539	8.10	57.9
6	39–41.5	1.4639	1.4659	+55.2	.8537	1.14	58.1
7	41.5–48	1.4666	1.4669	+36.6	.8407	1.00	58.3
8	48–48.5	1.4683	1.4689	+16.6	.8128	0.80	58.5
9	48.5–49.5	1.4683	1.4681		.8011	0.74	58.7
10	49.5–51	1.4683	1.4689	+10.8	.7914	9.10	61.0
11	51–52.5	1.4689	1.4690	+15.8	.7965	4.06	62.0
12	52.5–53.5	1.4709	1.4699		.8065	1.34	62.4
13	53.5–54.5	1.4699	1.4701	+52.8	.8135	1.58	62.7
14	54.5–56	1.4708	1.4709	+84.9	.8288	1.94	63.2
15	56	1.4709	1.4718	+109.5	.8405	4.08	64.3
16	56–59.5	1.4718	1.4719	+108.8	.8419	1.50	64.6
17	59.5–64	1.4719	1.4749	+65.7	.8563	1.11	64.9
18	64–91	1.4749	1.4799	−1.9	.9194	3.07	65.6
19	91–98.5	1.4799	1.4758	+57.3	.9636	3.71	66.6
20	98.5–101.5	1.4692	1.4699	+44.5	.9638	3.46	67.5
21	101.5–104	1.4734	1.4740	+34.1	.9581	1.13	67.7
22	104–110.5	1.4741	1.4779	+14.4	.9369	2.62	68.5
23	110.5–116.5	1.4786	1.4829	+0.8	.9165	1.53	68.9
24	116.5–118.5	1.4839	1.4873	0	.9134	1.72	69.3
25	118.5–121.5	1.4895	1.4934	0	.9117	0.94	69.6
26	121.5–125	1.4964	1.4984	+0.9	.9119	2.12	70.3
27	125–127	1.4984		+6.9	.9162	3.04	70.8
28	127–129	1.5009	1.5032	+23.2	.9182	1.77	71.3
29	129–137.5	1.5032	1.5039	+39.6	.9228	3.75	72.3
30	137.5–141.5	1.5039	1.5010	+14.0	.9383	0.95	72.5
31	141.5–142.5	1.5014	1.5009		.9501	0.77	72.7
	5 mm.						
32	125.5–127.5	1.4999	1.5009	+3.0	0.9551	1.54	73.1
33	127.5–134.5	1.5009	1.5009	+3.5	0.9642	4.66	74.2
34	134.5–135.5	1.5014	1.5024	+5.5	0.9659	3.95	75.2
	0.01 mm.						
35	100–112		1.5085	+3.1	0.9788	6.60	76.9
36	107		1.5110			0.79	77.1
37	110		1.5133		0.9721	2.34	77.7
38	116–127		1.5176		0.9714	5.20	79.0
39	116–127		1.5183		0.9707	3.38	79.8
40	116–127		1.5178			2.34	80.4
41	Residue					46.30	93.3
	Loss					26.70	100.0

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* The rotations of fractions 1–5 were measured at 25°, the remainder at room temperature which varied from 20–23°.

Fraction 18 with a maximum in the refractive index and a minimum in the optical rotation was refractionated through a microcolumn (10). Two compounds clearly existed but were too small to be identified or characterized.

The ester number of fractions 19 and 20 indicated the presence of 40–50% of ester (calculated as the acetate of $C_{10}H_{18}O$). From the saponified material *d*-borneol was isolated and identified by mixed melting point, while the absence of formic and the presence of acetic acid was indicated by color tests. Thus the ester present is probably bornyl acetate, and the physical constants of fraction 20 are in approximate agreement.

From fractions 25–29, A4, and A5, a total of 30 mg. of a solid, m.p. 148–149°, crystallized, which is most probably optically active sobrerol, but no authentic specimen was available for identification by mixed melting point. It probably arose by autoxidation of the *d*-α-pinene on standing (11) since the essential oil had been preserved for some years before distillation.

TABLE II

REFRACTIONATION OF FRACTIONS 23 TO 29

FRACTION	B.P./10 MM °C	n_D^{25} 1ST DROP	n_D^{25}	$[\alpha]_D^{23}$ IN MICRO TUBE	d_4^{25}	WEIGHT, G
A1	(108)–112–114	1.4798	1.4809	−ve	0.9245	0.50
A2	114–116	1.4810	1.4833	−2	.9131	0.89
A3	116–118.5	1.4837	1.4862	−ve	.9126	1.67
A4	118.5–121	1.4888	1.4890	−1	.9107	0.79
A5	121–122	1.4900	1.4922	−1	.9168	1.13
A6	122–125	1.4922	1.4939	−2	9168	0.88
A7	125–127	1.4969	1.4994	−4	.9179	1.21
A8	127–129	1.4995	1.5030	+9	.9241	1.02
A9	129–129.5	1.4979	1.5003	+6	.9252	0.79
A10	129–129.5	1.5003	1.5013	+16	.9262	0.65
A11	129–129.5	1.5017	1.5032	+42	.9234	1.01
A12	129.5–130	1.5035	1.5055	+60	.9239	0.77
A13	130–131	1.5055	1.5055	+53	.9270	0.58

Fractions 23–29, whose physical constants agreed with a sesquiterpene range, were refractionated at 10 mm., the results of which are recorded in Table II. The high density of fraction A1 indicated an oxygenated impurity and the presence of carvone was established by the preparation of its 2,4-dinitrophenylhydrazone, undepressed in melting point with an authentic specimen.

Dehydrogenation of fractions A3–A7 with palladium charcoal gave a small yield of an azulene while, in addition, from fraction A7 alone, cadalene trinitrobenzolate was obtained and identified by mixed melting point. The azulene was isolated by Sherndal's method (12), and formed a trinitrobenzolate, m.p. 140–141.5°, in amount too small for further purification but which we consider is S-guaiazulene since the melting point was raised by an authentic specimen.

Fractions A8–A13 were mainly cadinene, cadalene picrate being prepared from fraction A11 in 49% yield and *l*-cadinene dihydrochloride in 60% yield from fraction A12.

It would appear that fractions A3–A6 contain a tricyclic sesquiterpene, with $[R_{L_D}]$ 64.22$\sim$64.79; calc'd 64.40, the physical constants agreeing most closely with those of copaene and α-santalene. Since neither of these, however, furnishes azulene on dehydrogenation, the low-boiling sesquiterpene in this oil is probably new.

From a consideration of their physical properties, the action of dry hydrogen chloride, and the results of dehydrogenation with palladium-charcoal on fractions 31–37 it is apparent that at least three sesquiterpene alcohols are present. Fractions 31–37 do not yield solid 3,5-dinitrobenzoates nor urethans, but the azulene from fractions 32–33 forms a trinitrobenzolate, m.p. 150–151.5°, identified with that of S-guaiazulene.

After long standing in the refrigerator, fraction 34 deposited 140 mg. of a solid, m.p. 42–43°, after purification by sublimation *in vacuo*. Analysis showed it to be a sesquiterpene alcohol, $C_{15}H_{25}OH$, which may be new, since the combined physical properties and dehydrogenation products of fractions 31–34 do not agree with any known compound. Elemol (13, 14) is the only sesquiterpene alcohol of similar melting point, values 42° to 52° being recorded, but whereas it gives eudalene on dehydrogenation with selenium, fraction 34, from which the solid alcohol had separated gives an azulene and *l*-cadinene dihydrochloride (a trace of the latter was also obtained from fraction 33). Elemol also is monocyclic whereas the constants of fraction 34 indicate a dicyclic compound.

From fraction 37 an azulene was obtained on dehydrogenation in amount too small for characterization.

Fraction 35, whose density is at a peak, furnished *l*-cadinene dihydrochloride, and cadalene on dehydrogenation with palladium-charcoal but no azulene. The physical constants of this dicyclic sesquiterpene alcohol do not agree with those of any of the cadinols already isolated.

Fractions 38–40 partly solidified on cooling, the solid being identified as phyllocladene by mixed melting point and conversion to isophyllocladene. Phyllocladene was also isolated in the last fraction of the steam distillation of the original oil (6).

The residue, m.p. 88–90°, from the final distillation (Table I) on extraction with boiling alcohol gave a trace of phyllocladene but it was almost completely insoluble in organic hydroxylic solvents, non-volatile in steam, and failed to distil at 200° in a high vacuum. The molecular weight of 500–600, estimated ebullioscopically in benzene, indicated a polymerized product possibly due to the myrcene present [*cf.* the formation of α-camphorene (15)] or to the long period of heating inherent in the distillation process.

EXPERIMENTAL

Leaves and terminal branchlets of *Dacrydium kirkii* were collected in September and November at Waipoua Forest and supplied by Mr. Saxton through courtesy of the State Forestry Department, to whom we express our grateful thanks. The oil obtained on steam distillation in the usual way had been dried and stored in dark well-stoppered bottles away from direct light for four years before the present investigation.

The physical and chemical constants were determined by standard methods, ester numbers according to methods recommended by the Essential Oil Sub-Committee of the Society of Public Analysts and other Analytical Chemists (16). Distillation was effected by a Bower and Cooke column (7) using a gold-plated brass spiral in the absence of the recommended one of Monel metal. The still-pot consisted of an electrically heated hemispherical oil-bath while the still-head was of the total reflux, variable take-off type using a chromium-plated copper reflux condenser greatly exceeding the efficiency of the normal glass type. Even so appreciable losses occurred in the initial stages but were minimized subsequently by the use of ice-water. The pressure was maintained constant by an electrically controlled manostat. For the separation of the sesquiterpene alcohols from the diterpenes, a modified Craig column was used, 20 cm. long, without condenser, with a side arm dipping into a series of rotating receivers. The results of the first distillation are recorded in Table I, those of the refractionation of the sesquiterpenes in Table II.

α-Pinene. Fraction 1 on oxidation with neutral permanganate according to Delépine (17) yielded 49% of crude pinonic acid, purified by distillation, b.p. 155–162°/5 mm. The crystals, which separated on cooling, after recrystallization from light petroleum (b.p. 50–60°) had $[\alpha]^{25}_{D}$ +92.6° (c = 2.5 in chloroform), m.p. 69–70°, not depressed by an authentic specimen. Delépine records m.p. 69–70°, $[\alpha]_D$ +93.5°.

Myrcene. An exothermic reaction occurred on mixing fraction 10 (1.5 g., 1 mole) with maleic anhydride (0.99 g., 1 mole). Distillation at 10 mm. removed a little unchanged terpene, followed by the adduct, b.p. 196–197°, m.p. 33–34° (yield 86%). The acid obtained on hydrolysis, after crystallization from acetonitrile, had m.p. 123–124°, undepressed by an authentic specimen. Diels and Alder (18) record 33–34° for the anhydride, m p 122–123° for the acid.

Limonene. Bromination of Fraction 15 with bromine in either glacial acetic acid or an amyl alcohol-ether mixture gave poor yields (9 and 15% respectively) of the corresponding tetrabromo derivative, m.p. 104° after crystallization from ethyl acetate, and undepressed by an authentic specimen. Other investigators have also experienced low yields (19).

Bornyl acetate. Determinations of the saponification number of fractions 19 and 20 gave values of 41 and 49% of ester respectively (calculated as $C_{10}H_{17}OCOCH_3$). The hydrolyzed oil (200 mg.) on standing for a month deposited a small quantity of platelets with a pronounced camphoraceous odor. After purification by vacuum sublimation and crystallization from light petroleum they had m.p. 208° (sealed tube) undepressed by pure *d*-borneol. Color tests for the formate ion with resorcinol and pyrogallol (20) with a further saponified sample were negative. However, after evaporating a sample to dryness with lime and dry distillation, a positive test for acetone (and therefore acetic acid originally) was given by the formation of a blue color on a filter paper saturated with an alkaline solution of *o*-nitrobenzaldehyde, intensified by the addition of a drop of dilute hydrochloric acid (21). The alcohol number of fractions 19–22 showed the presence of alcohols in amount not exceeding 20%.

Carvone. Only fraction 23 of fractions 18–29 gave a positive test with Brady's reagent. The small red precipitate, after crystallization from alcohol, had m.p. 187–188°, undepressed by an authentic specimen of carvone 2,4-dinitrophenylhydrazone (22).

Sobrerol. The solid (30 mg.) separating from fractions 25–27 was soluble in all common organic solvents except light petroleum, and hot or cold water. After purification by vacuum sublimation it had m.p. 148–149°.

Anal. Calc'd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66.
Found: C, 70.53, 70.65; H, 10.41, 10.65.

As an alcohol it reacts with sodium with gas evolution and appears to be identical with optically active sobrerol whose melting point Armstrong and Pope (23) record as 148–149°. The amount of pure material isolated was too small for the preparation of a derivative.

Sesquiterpene fractions. Fraction A6 (430 mg.) and palladium charcoal were maintained at 260–280° for 17 hours, to give on distillation 130 mg. of a deep blue oil, b.p. 120–160°/10 mm., and a considerable residue. The azulene, extracted with 85% phosphoric acid (Sherndal's method) was isolated by the addition of ice-water and solution in light petroleum (b.p. 40–50°) to give 10 mg. of an intense blue oil, which on refluxing with trinitrobenzene in absolute alcohol gave a brown crystalline product, m.p. 115°, raised to m.p. 140–141.5°

after four crystallizations from absolute ethyl alcohol, when the amount became too small for further purification. The melting point, however, was raised by the same derivative of S-guaiazulene, with which it is probably identical. No picrate-forming substance was isolated from the non-azulenic oil.

Fractions A3–A7 (2.61 g.) and palladium charcoal (250 mg.) were maintained at 260–280° for 7 hours. On distillation 1.05 g. of blue oil was obtained, b.p. 120–170°/10 mm., and extraction by Sherndal's method gave 36 mg. of azulene. From the non-azulenic portion cadalene was isolated as its trinitrobenzolate, m.p. 112–113°, undepressed by an authentic sample (25). The cadalene must have arisen from fraction A7 since neither A6 nor any of the lower fractions gave cadalence on dehydrogenation.

Fraction A11 (400 mg.) and palladium charcoal (50 mg.) were maintained at 186° for 6.5 hours. After filtration from the catalyst the oil was treated with excess picric acid. The picrate-forming oil (180 mg.), regenerated in the usual way, was treated with picric acid (210 mg.) in ethyl alcohol to give cadalene picrate, m.p. 112–113°, not depressed by an authentic sample.

Fraction A12 (450 mg.) in dry ether (3 cc.) was saturated with dry hydrogen chloride. The homogeneous needles (270 mg.) separating out on evaporation, after recrystallization from ethyl acetate, had $[\alpha]_D^{25}$ −36.8° (c = 2 in chloroform) and m.p. 117–118°, undepressed by an authentic sample of *l*-cadinene dihydrochloride.

Sesquiterpene alcohols. One hundred forty milligrams of a solid alcohol was isolated from fraction 34 after standing in a refrigerator for some time. It was very soluble in most of the common organic solvents and was purified by vacuum sublimation at 110°/6 mm. to m.p. 42–43°.

Anal. Calc'd for $C_{15}H_{26}O$· C, 81.08; H, 11.71.

Found: C, 80.87; H, 11 47.

Fraction 33 (400 mg.) in dry ether was saturated with dry hydrogen chloride. After removal of the solvent and solution in ethyl acetate it was allowed to stand for three months, when a few milligrams of *l*-cadinene dihydrochloride was obtained, m.p. 118°, undepressed by an authentic sample.

Fractions 34 (90 mg.) and 35 (41 mg.) similarly gave *l*-cadinene dihydrochloride, 14 mg. (14%) and 15 mg. (32%) respectively.

Fraction 37 gave only a liquid hydrochloride using the method outlined above.

Fraction 32 (340 mg.) and palladium-charcoal (30 mg.) were heated to 200–230° for 8 hours. The product was distilled to give 160 mg. of a blue oil from which no cadalene trinitrobenzolate could be isolated.

Fractions 32–33 (2.43 g.) and palladium-charcoal (250 mg.) were maintained at 200° until water ceased to be evolved, then at 260–300° for 7 hours. After distillation, the product, 1.2 g., b.p. 120–160°/10 mm , was extracted by Sherndal's method and gave 179 mg. of azulene.

The crude trinitrobenzolate obtained therefrom had m.p. 114°, and after eight crystallizations from absolute alcohol melted constantly at 150–151.5°. The melting point was not depressed by an authentic specimen of S-guaiazulene trinitrobenzolate (24) kindly provided by Professor Plattner. From the non-azulenic portion 40 mg. of cadalence trinitrobenzolate, m.p. 112–113°, was obtained (25).

Fraction 35 (600 mg.), on dehydrogenation with palladium-charcoal (60 mg.), gave 380 mg. of a colorless oil which on distillation gave 180 mg. of oil, b.p. 158–160°/10 mm., forming cadalene trinitrobenzolate, m.p. 112–113°, in good yield.

Fraction 37 (49 mg.) on dehydrogenation with palladium charcoal gave 24 mg. of a light blue oil from which no cadalene as the trinitrobenzolate could be isolated.

Phyllocladene. The solid (2.5 g.) separating out from fractions 38–40, after three crystallizations from methyl alcohol had $[\alpha]_D^{25}$ +16° (c = 3.5 in chloroform) and melted at 95–96°, not depressed by an authentic specimen. The identity was confirmed by isomerization with methyl alcoholic sulfuric acid to isophyllocladene which, after recrystallizations from methyl alcohol, had m.p. 109–110°, undepressed by an authentic sample.

All melting points are uncorrected. The analyses are by J. Mills, University of Adelaide.

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SUMMARY

The essential oil from the leaves of *Dacrydium kirkii* has been shown to consist of the following constituents expressed in approximate percentages:

1. Terpenes: *d*-α-pinene, 65%; myrcene, 4%; *d*-limonene, 2%; unidentified, 2%.
2. Sesquiterpenes: unidentified sesquiterpene, b.p. 118–125°/10 mm., 1.5%, cadinene, 1%.
3. Diterpene: phyllocladene, 1%.
4. Alcohols: unidentified sesquiterpene alcohols: (a) b.p. 125–134°/5 mm. 4%; (b) m.p. 42–43°, b.p. 135°/5 mm., a trace; (c) b.p. 100–112°/0.01 mm., 1.5%.
5. Ester: *d*-bornyl acetate, 1%.
6. Ketone: carvone, a trace.
7. Other compounds, including residue, 17%.

The sesquiterpene alcohol, m.p. 42–43°, is probably new.

AUCKLAND, NEW ZEALAND

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ACETOMORPHINE AND ACETOCODEINE

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The introduction of an acetyl group into the aromatic ring of morphine and codeine by the action of sulfoacetic acid, $HOSO_2CH_2COOH$ (1), was first described in a patent of Knoll and Co. (2). Later, Knorr (3) prepared various derivatives of acetocodeine, degraded it to aceto-β-methylmorphimethine, and ultimately to acetomethylmorphol. More recently, Small and Mallonee (4) proved by way of the Beckmann rearrangement of aceto-6-acetylcodeine oxime, that the acetyl ("aceto") group occupies the 1-position. It is convenient to retain the term "aceto" for this group to distinguish it from O-acetyl groups.

The present communication concerns reduction products of acetomorphine, acetocodeine, and their derivatives, which were prepared primarily for pharmacological study, in continuation of the program initiated in 1929 by the Committee on Drug Addiction of the National Research Council.

Treatment of anhydrous dihydrocodeine (I) with sulfoacetic acid results in 1-aceto-6-acetyldihydrocodeine (II) in excellent yield. As would be expected, the same compound is obtained by hydrogenation of 1-aceto-6-acetylcodeine (III) with palladium. Under more vigorous conditions, in acid solution with platinum oxide, the reduction proceeds further, and the aceto group is attacked. Two products are obtained, 1-(1-hydroxyethyl)-6-acetyldihydrocodeine (IV), and 1-ethyl-6-acetyldihydrocodeine (V). Reduction of 1-aceto-6-acetyldihydrocodeine (II) with aluminum in ethanol and ether also gives IV.

Catalytic reduction of the hydrolysis product, 1-acetocodeine (VI), likewise gives rise to products of different stages of reduction, according to the conditions. With palladium, 1-acetodihydrocodeine (VII) is obtained, whereas platinum gives 1-(1-hydroxyethyl)dihydrocodeine (VIII) and 1-ethyldihydrocodeine (IX). The latter is not crystalline, but can be identified by acetylation to V.

In order to obtain reduction products in which the alicyclic double bond is intact it is necessary to use metallic agents. Reduction of 1-acetocodeine with Raney nickel-aluminum alloy in alkali by the procedure of Papa, Schwenk, and Whitman (5) gives a complex mixture, from which a small amount of 1-acetodihydrocodeine (VII) can be isolated. Reduction with amalgamated aluminum is also not simple, but gives a fair yield of 1-(1-hydroxyethyl)codeine (X). The parallel reduction of 1-aceto-6-acetylcodeine (III) results in 1-(1-hydroxyethyl)-6-acetylcodeine (XI).

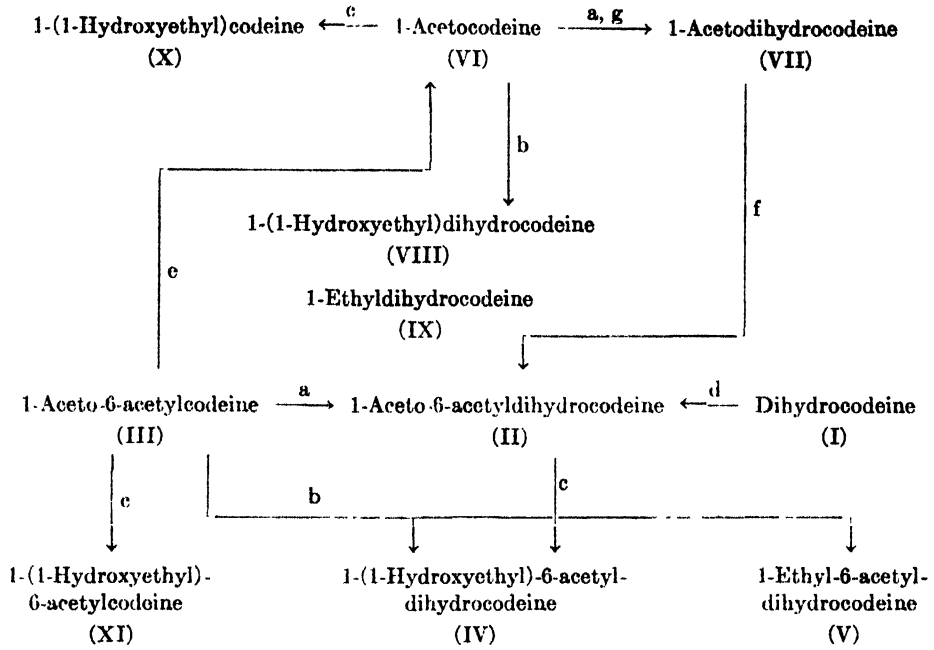
The relationships of these various reduction and hydrolysis products are summarized in Chart I.

THE 1-ACETOMETHYLMORPHIMETHINES

Incidental to the study of 1-acetocodeine derivatives, we became interested in Knorr's curious observation that the product from the first step of the Hofmann degradation is an aceto-β-methylmorphimethine; if his conclusion is correct, it is the only example in morphine chemistry of a shift of the 7,8-unsaturation to the 8,14-position *during* the degradation. He based his assumption of the β-structure on the fact that he was unable to effect a rearrangement in the sense of the α- to β-methylmorphimethine transformation; further, on the dextro rotation, +150°, analogous to β-methylmorphimethine, +438°, rather than to α-methylmorphimethine, −212°. Both observations are indicative, but not conclusive.

CHART I

Reduction Products of 1-Acetocodeine

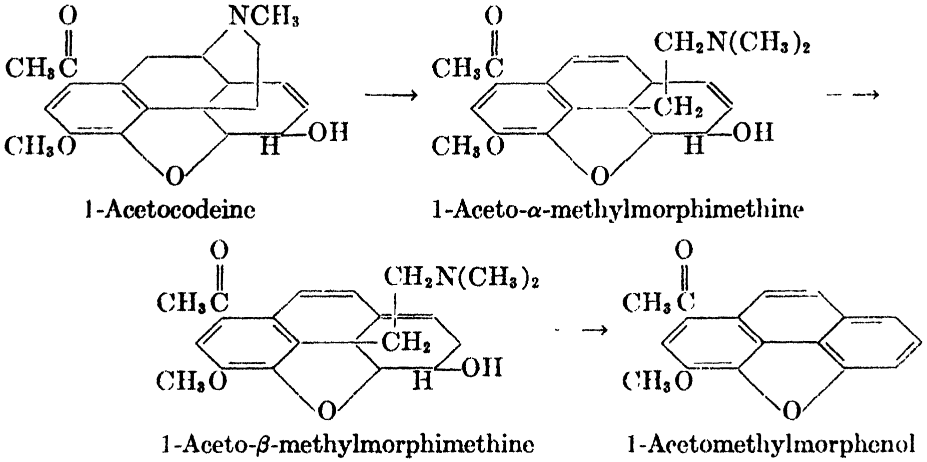

1-(1-Hydroxyethyl)codeine
(X)
c
1-Acetocodeine
(VI)
a, g
1-Acetodihydrocodeine
(VII)
b
f
e
1-(1-Hydroxyethyl)dihydrocodeine
(VIII)
1-Ethyldihydrocodeine
(IX)
1-Aceto-6-acetylcodeine
(III)
a
1-Aceto-6-acetyldihydrocodeine
(II)
d
Dihydrocodeine
(I)
c
b
c
1-(1-Hydroxyethyl)-6-acetylcodeine
(XI)
1-(1-Hydroxyethyl)-6-acetyldihydrocodeine
(IV)
1-Ethyl-6-acetyldihydrocodeine
(V)

a. Reduction with palladium
b. Reduction with platinum
c. Reduction with aluminum
d. Sulfoacetic acid
e. Hydrolysis
f. Acetic anhydride in pyridine
g. Raney alloy in alkali

If the hypothesis is accepted, that the α- to β-rearrangement results from a tendency to form a conjugated system with the 9,10-unsaturation and the aromatic ring, it might be argued that increasing the length of the conjugated system by the carbonyl group at the 1-position would increase this tendency, and thus explain this anomalous reaction.

Attempts to verify the Knorr structure by the action of sulfoacetic acid on α- or β-methylmorphimethine gave black tars. At this point, we sought for structural evidence by comparing the ultraviolet absorption spectrum of Knorr's product with that of authentic β-methylmorphimethine (Fig. 1), but the disturbing influence of the 1-aceto group made this inconclusive. It was found, however, that if the alkaline degradation of 1-acetocodeine methiodide was heated for only five minutes, instead of fifteen as described by Knorr, a good yield of 1-aceto-α-methylmorphimethine was obtained. The α structure for the new product is evident, for it gave on short heating with alcoholic KOH a 90% yield of the β compound which results from the Knorr procedure. In Fig. 2 are shown the spectra of the new α-compound and of α-methylmorphimethine.

Knorr completed the degradation of the β-methine by a drastic sealed-tube reaction with sodium ethoxide, obtaining 1-acetomethylmorphol; he apparently did not attempt, or was unsuccessful in, the alkaline degradation of the methiodide. 1-Aceto-β-methylmorphimethine methiodide evolves no trimethylamine


1-Acetocodeine

1-Aceto-α-methylmorphimethine

1-Aceto-β-methylmorphimethine

1-Acetomethylmorphenol

with aqueous or alcoholic alkali. Dry distillation of the methohydroxide in a high vacuum yields a small amount of non-phenolic, nitrogen-free compound, which on the basis of analysis is assumed to be the expected 1-acetomethylmorphenol. Application of the Mosettig and Meitzner (6) sodium cyclohexoxide method results in copious evolution of trimethylamine, but the product is an undistillable liquid which yields no trace of crystalline semicarbazone. We surmise that polymerization involving the aceto group takes place in this degradation.

1-ACETOMORPHINE AND REDUCTION PRODUCTS

Manipulation and transformations in the acetomorphine series are more difficult than with acetocodeine, and the results are not as complete. The action of sulfoacetic acid on dihydromorphine (XII) apparently results in 1-aceto-3,6-diacetyldihydromorphine (XIII), which is (fortunately) half-hydrolyzed by ammonia in the subsequent operations, yielding the well-defined 1-aceto-6-acetyldihydromorphine (XIV). Catalytic hydrogenation (one mole of hydrogen)

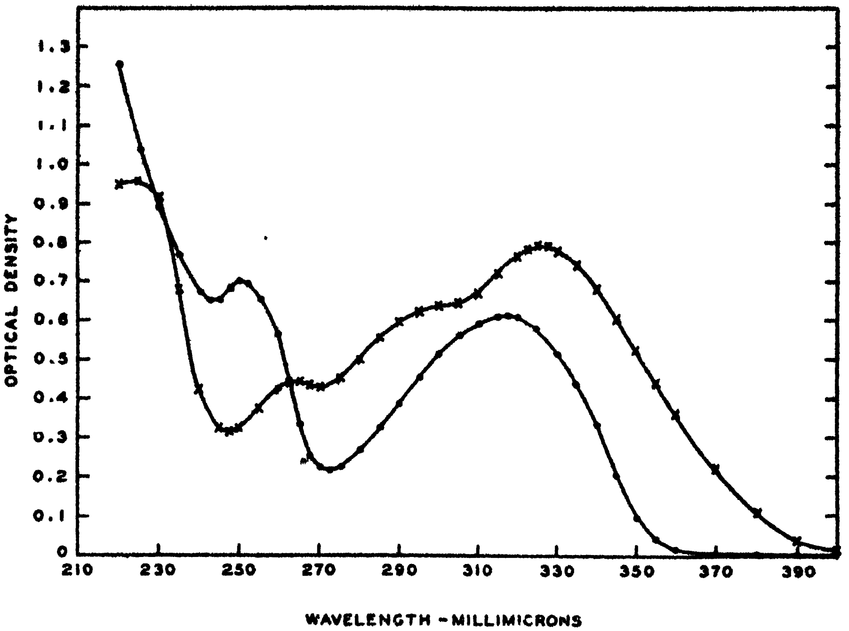


Fig. 1. Ultraviolet Absorption Spectra

-●-●- β-Methylmorphimethine 0.019 mg./ml., 95% alcohol.
-✱-✱- 1-Aceto-β-methylmorphimethine, 0.019 mg /ml., 95% alcohol.

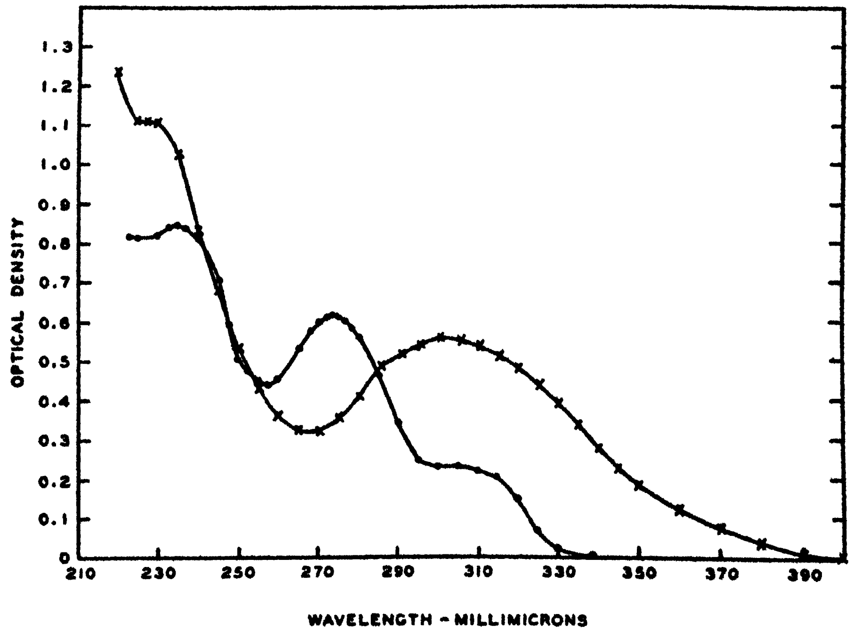


Fig. 2. Ultraviolet Absorption Spectra

-●-●- α-Methylmorphimethine, 0.019 mg./ml., 95% alcohol.
-✱-✱- 1-Aceto-α-methylmorphimethine, 0.019 mg./ml., 95% alcohol.

of 1-aceto-3,6-diacetylmorphine (XV, *ex* morphine and sulfoacetic acid) gives a colorless glass (XIII), as does reacetylation of XIV; it appears to form no crystalline salts, but can be purified by high-vacuum distillation. Complete hydrolysis of XIV with sodium ethoxide results in considerable decomposition, and intractable products.

Probably because of the activating effect of the 7,8-unsaturation upon groups in the 6-position, 1-aceto-3, 6-diacetylmorphine (XV) cannot be hydrolyzed stepwise. Hydroxylamine, which gives excellent yields of 6-acetylmorphine from 3,6-diacetylmorphine (7) is of course excluded. Cold concentrated ammonia, in contrast to its action in the reduced series, removes both O-acetyl groups, giving 1-acetomorphine (XVII). Palladium hydrogenation of XVII gives a resinous product, presumably identical with that from the hydrolysis of XIV.

CHART II

Reduction Products of 1-Acetomorphine

$$\begin{tikzcd}
\begin{array}{c}\text{Dihydromorphine}\\ \text{(XII)}\end{array} \arrow[r, "a"] & \begin{array}{c}\text{1-Aceto-6-acetyl-}\\ \text{dihydromorphine}\\ \text{(XIV)}\end{array} \arrow[r, "b"] \arrow[d, shift right, "c"'] & \begin{array}{c}\text{1-Aceto-6-acetyl-}\\ \text{dihydrocodeine}\\ \text{(II)}\end{array} \\
\begin{array}{c}\text{1-Aceto-3,6-diacetylmorphine}\\ \text{(XV)}\end{array} \arrow[r, "f"] \arrow[d, "e"] & \begin{array}{c}\text{1-Aceto-3,6-diacetyldihydromorphine}\\ \text{(XIII)}\end{array} \arrow[u, shift right, "d"'] & \\
\begin{array}{c}\text{1-Acetomorphine}\\ \text{(XVII)}\end{array} \arrow[rr, "b"] & & \begin{array}{c}\text{1-Acetocodeine}\\ \text{(VI)}\end{array}
\end{tikzcd}$$

a. Sulfoacetic acid
b. Diazomethane
c. Acetic anhydride in pyridine
d. Half hydrolysis (ammonia)
e. Complete hydrolysis (ammonia)
f. Reduction with palladium

It is reasonable to assume that the nuclear acetyl group in the acetomorphine series occupies the same position as that of the acetocodeine series. The validity of this assumption is established by methylation of 1-acetomorphine (XVII) and 1-aceto-6-acetyldihydromorphine (XIV) to their respective codeine analogs, VI and II.

The relationships of the acetomorphine derivatives are summarized in Chart II.

The physiological action of the more accessible compounds described in this paper has been studied by Dr. N. B. Eddy and will be reported in the pharmacological literature.

ACKNOWLEDGMENTS

We are indebted to Dorothy Peterson of the Industrial Hygiene Laboratory for the absorption spectra, and to Luther Modlin, C. A. Kinser, and Betty Mount for microanalyses. One of us (J. E. M.) was the recipient of the Mallinckrodt Fellowship in Alkaloid Chemistry.

EXPERIMENTAL

Sulfoacetic acid. As used in the following experiments, this was prepared by heating 1 part (wght.) of conc'd sulfuric acid with 8 parts of acetic anhydride at 85° for 10 minutes. Freshly distilled anhydride should be used to avoid development of red coloration; test for sulfate was negative (see ref. 8).

1-Acetocodeine (VI). Knorr (3) apparently did not recognize that this compound is hydrated. It melts at 149–150°, but in a plunge melting point at 130°, melts with vigorous gas evolution.

Anal. Calc'd for $C_{20}H_{23}NO_4+H_2O$: H_2O, 5.01.
Found: loss at 100° in a vacuum, 5.02.

1-Aceto-6-acetylcodeine (III) was prepared in 30-g. codeine batches according to the patent procedure (2), in crude yields of 90–95%; in preparations carried out in 1938, the product purified from alcohol showed the m.p. 146–147°. Eight years later, in a different Laboratory, a form was obtained which melted at 125–126.5°, and apparently contained one-half molecule of hydrate water (calc'd 2.3%, loss at 100°, 2.7%). The dried material also melted at 125–126.5°, and is an unstable modification; on grinding with a trace of the 146° form, it had the m.p. 146–147°. For low-melting anhydrous form, $(\alpha)_D^{20}-208°$; for high-melting form, $(\alpha)_D^{20}-207°$ (U.S.P. chloroform).

1-Aceto-6-acetyldihydrocodeine (II). Anhydrous, vacuum-distilled dihydrocodeine, 16 g., was added rapidly to 130 ml. of sulfoacetic acid at 85°, and held at this temperature for 8 minutes. It was cooled quickly, poured onto ice, and the base was precipitated crystalline with ammonia, yield 16 g. (88%), m.p. 160–163°; from ethyl acetate, m.p. 166–167°. The same compound was obtained when 1-aceto-6-acetylcodeine (10 g.) was hydrogenated (1 mole, 3.5 hours) in 50 ml. of 5% acetic acid with 10 ml. of 1% palladous chloride solution, yield 9 g. It also resulted (88% yield) when 1-acetodihydrocodeine (VII) was acetylated with acetic anhydride and pyridine. In acetone, $(\alpha)_D^{20}-105°$ (*c*, 1.00).

Anal. Calc'd for $C_{22}H_{27}NO_5$: C, 68.6; H, 7.06.
Found: C, 68.7; H, 6.87.

1-(1-Hydroxyethyl)-6-acetyldihydrocodeine (IV). A solution of 5 g. of 1-aceto-6-acetylcodeine in 30 ml. of 2 *N* hydrochloric acid with 150 mg. of platinum oxide absorbed 2.7 moles of hydrogen in 3 days. The catalyst-free solution was covered with a thin layer of ether, and excess sodium carbonate solution added. The hydroxyethyl derivative precipitated crystalline (0.7 g.) and was purified from alcohol; m.p. 251–252° (evac. tube, decomp.). It forms a crystalline tartrate of very indefinite melting point, probably hydrated. In U.S.P. chloroform the base shows $(\alpha)_D-91.2°$ (*c*, 1.01).

Anal. Calc'd for $C_{22}H_{29}NO_5$: C, 68.2; H, 7.54.
Found: C, 68.2; H, 7.31.

The same compound was obtained when 1-aceto-6-acetyldihydrocodeine (10 g.) in ether and ethanol (1:1) was reduced with amalgamated aluminum groats (6 g.) for 5 days. The yield was 1.6 g. The remaining material (7.2 g.) obtained on concentration was resinous; 25% of it was the hydroxyethyl compound, separated by high-vacuum sublimation. An unidentified compound of m.p. 150–160° was present in small amount (about 15%).

1-Ethyl-6-acetyldihydrocodeine (V). The alkaline mother liquor from which the hydroxyethyl compound had been precipitated (catalytic hydrogenation) was saturated with potassium carbonate and extracted with ether. The ether left 4.5 g. of oily base, which was converted to the acid tartrate (4.8 g.) in acetone with conc'd aqueous tartaric acid. The tartrate was recrystallized from water; it was hydrated, and the melting point was very indefinite, about 160–170°.

Anal. Calc'd for $C_{26}H_{35}NO_{10}+H_2O$: C, 57.9; H, 6.90; H_2O, 3.3.
Found: C, 58.0; H, 7.01; H_2O, 4.0.

The base liberated from the tartrate was recrystallized from 60% alcohol; m.p. 104.5–105.5°; $(\alpha)_{D}^{20}-126°$ (alcohol, *c*, 1.001).

Anal. Calc'd for $C_{22}H_{29}NO_4$: C, 71.1; H, 7.86.
Found: C, 71.2; H, 7.92.

1-(1-Hydroxyethyl)dihydrocodeine (VIII). A solution of 5 g. of acetocodeine in 50 ml. of normal hydrochloric acid with 140 mg. of platinum oxide took up 2.7 moles of hydrogen in 2 days. Conc'd ammonia precipitated an oil which was extracted into ether. On standing, the ether and aqueous portion both deposited crystals. The 3 g. of sticky crystals from ether was triturated with isopropyl ether, leaving a residue of 1.6 g. of crystals melting below 100°, probably a mixture of the 1-ethyl and 1-(1-hydroxyethyl) compounds. The isopropyl ether gave 1.4 g. of oil, 1-ethyldihydrocodeine, identified by acetylation to 1-ethyl-6-acetyldihydrocodeine, m.p. 103–105°.

The crystals from the water layer, 0.8 g., with 0.7 g. obtained by saturation with potassium carbonate, were recrystallized from 60% alcohol (short rods), and sublimed twice at 145° in a high vacuum; m.p. 225–227° (evac. tube); $(\alpha)_{D}^{20}-82.0°$ (10% acetic acid, *c*. 0.72).

Anal. Calc'd for $C_{20}H_{27}NO_4$: C, 69.5; H, 7.88.
Found: C, 69.4; H, 8.10.

1-(1-Hydroxyethyl)-6-acetylcodeine (XI). A solution of 5 g. of 1-aceto-6-acetylcodeine in ether and ethanol (1:1) was reduced with amalgamated aluminum groats during four days. The precipitate was filtered and washed with hot alcohol. Solvent was removed, and the oil remaining was converted to the tartrate (5 g.) in acetone with aqueous tartaric acid. From the mother liquors of the tartrate preparation, 1.4 g. of poorly crystalline base was isolated. This was purified from 60% alcohol, giving 1-(1-hydroxyethyl)-6-acetylcodeine, m.p. 185–187°; $(\alpha)_{D}^{20}-212°$ (U.S.P. $CHCl_3$, *c*, 0.302).

Anal. Calc'd for $C_{22}H_{27}NO_5$: C, 68.6; H, 7.06.
Found: C, 68.4; H, 7.08.

The above acid tartrate of the hydroxyethyl compound was difficult to purify; six crystallizations from water gave an analytical sample, hydrated, sintering at 150° and melting at 165–170°; $(\alpha)_{D}^{20}-115°$ (water, *c*, 0.307).

Anal. Calc'd for $C_{26}H_{35}NO_{11}+H_2O$: C, 56.4; H, 6.36; H_2O, 3.3.
Found: C, 56.6; H, 6.36; H_2O, 3.4.

1-(1-Hydroxyethyl)codeine (X). An excess of amalgamated aluminum groats was added to a solution of 2 g. of 1-acetocodeine in 200 ml. of ether with 20 ml. of ethanol and allowed to react for 24 hours. The aluminum ethoxide sludge was removed and washed well with alcohol. Concentration under diminished pressure gave a mixture of oil and crystals. This was triturated with 50 ml. of acetone; yield 0.4 g. of white crystals, m.p. 222–224° (evac. tube) after 3 crystallizations from alcohol and sublimation in a high vacuum at 140°. In alcohol, $(\alpha)_{D}^{20}-101°$ (*c*, 0.417).

Anal. Calc'd for $C_{20}H_{25}NO_4$: C, 69.9; H, 7.34.
Found: C, 70.1; H, 7.10.

Treatment of the acetone liquor with aqueous tartaric acid gave 1.4 g. of salt, which was difficult to purify (80% acetone–20% water) and yielded a negligible amount of the hydroxyethyl base.

1-Acetodihydrocodeine (VII). Sixteen grams of 1-acetocodeine in 50 ml. of 10% acetic acid with 10 ml. of 1% palladous chloride solution absorbed one mole of hydrogen in 5 hours. The solution was filtered through Norit and saturated with potassium carbonate. The heavy gum was extracted into benzene (insoluble in ether), which was concentrated, at the end under diminished pressure. The residue crystallized when rubbed with ethyl acetate; yield 15 g. (98%). Purified from this solvent, m.p. 138–140°. It sublimed amorphous at 150°/0.1 mm. In alcohol, $(\alpha)_{D}^{20}-101°$ (*c*, 1.05).

Anal. Calc'd for $C_{20}H_{25}NO_4$: C, 69.9; H, 7.34.
Found: C, 69.6; H, 7.32.

1-Acetodihydrocodeine (VII) *to* *1-aceto-6-acetyldihydrocodeine* (II). 1-Acetodihydrocodeine (1 g.) in 5 ml. of acetic anhydride with 1 ml. of pyridine was allowed to stand for 12 hours. The solution was concentrated in a vacuum at 50°, the red syrup taken up in water, and the base (II) was precipitated as sparkling crystals by cautious addition of normal ammonia; 87% yield, m.p. 166-167°.

1-Aceto-α-methylmorphimethine. Attempts to acetylate either α- or β-methylmorphimethine with sulfoacetic acid resulted in extensive decomposition, and black tars. A solution of 8.6 g. of acetocodeine methiodide in the minimum amount of boiling water was treated with 50 ml. of boiling 30% sodium hydroxide, and maintained at a gentle boil for 5 min. The brown resin was dissolved in 40 ml. of *N* HCl, decolorized, and precipitated crystalline with 3 *N* ammonia; yield 4.4 g. (70%). It is sparingly soluble in water, crystallizes from alcohol in large glassy prisms, m.p. 188–188.5° (evac. tube), 183–186° (red) in open tube. In U.S.P. chloroform, $(\alpha)_D^{20}$ 0.0° (*c*, 1.06), in 2.0 *N* acetic acid, $(\alpha)_D^{20}+12.6°$ (*c*, 1.19).

Anal. Calc'd for $C_{21}H_{25}NO_4$: C, 71.0; H, 7.09.
Found: C, 71.1; H, 7.24.

A solution of aceto-α-methylmorphimethine (1.2 g.) in 60% alcohol containing 10 % KOH was refluxed for 30 min. Removal of alcohol under diminished pressure caused separation of pale yellow crystals, which were purified from ethyl acetate, yield 1.1 g., 92%. The m.p. was 149°, in mixture with aceto-β-methylmorphimethine prepared according to Knorr, 149°; in U.S.P. chloroform, $(\alpha)_D^{20}+151°$ (*c*, 1.19); Knorr found $(\alpha)_D^{21}+150°$.

1-Acetomethylmorphenol. 1-Aceto-β-methylmorphimethine methiodide was prepared in the usual way, and purified from methanol; m.p. 273–276° (evac. tube, gas evol.). This salt has not been previously described.

Anal. Calc'd for $C_{22}H_{28}INO_4$: C, 53.1; H, 5.68.
Found: C, 52.7; H, 5.88.

Two grams of the methiodide was shaken for two hours in 20 ml. of water with the silver oxide from 3.4 g. of silver nitrate. The brown filtrate was evaporated in a vacuum to a brittle glass, which was heated at 200°/0.1 mm. About 200 mg. of white sublimate was obtained; insoluble in alkali, ferric chloride negative. It crystallized in long needles from ethyl acetate, m.p. 140.5°.

Anal. Calc'd for $C_{17}H_{12}O_3$: C, 77.2; H, 4.58.
Found: C, 76.8; H, 4.73.

1-Aceto-3,6-diacetylmorphine (XV). The patent (2) describing this product gives no analyses or optical data. A sample prepared according to the patent was recrystallized three times from alcohol and dried at 100°/0.1 mm.; loss negligible. In U.S.P. chloroform, $(\alpha)_D^{20}-207°$ (*c*, 1.10).

Anal. Calc'd for $C_{23}H_{25}NO_6$: C, 67 1; H, 6.12.
Found: C, 67.0; H, 6.05.

1-Aceto-6-acetyldihydromorphine (XIV). To 215 ml. of sulfoacetic acid at 85° was added 25 g. of anhydrous dihydromorphine at a rate which maintained this temperature, and the red solution was held at 85° for 30 minutes. It was cooled to 0°, and poured onto ice, and conc'd ammonia added slowly enough so that no resin precipitated (resin is probably the amorphous acetodiacetyl derivative). The resulting clear yellow solution crystallized rapidly, yield 19 g. (59%). It was purified from 300 ml. of methanol; m.p. 242° (decomp., evac. tube); $(\alpha)_D^{20}-97.2°$ (U.S.P. chloroform, *c*, 1.02)

Anal. Calc'd for $C_{21}H_{25}NO_5$: C, 67.9; H, 6.78.
Found: C, 67.7; H, 6.71.

1-Aceto-*6*-acetyldihydromorphine in ethereal diazomethane with a little methanol required 5 days for methylation, probably because of very low solubility. The product (II), purified from ethyl acetate, melted at 167.5°, mixed m.p. 167.5°.

1-Aceto-3,6-diacetyldihydromorphine (XIII). 1-Aceto-3,6-diacetylmorphine takes up one mole of hydrogen to give an oily product that is apparently 1-aceto-3,6-diacetyldihydromorphine, since it dissolves slowly in 3 *N* ammonia and deposits crystals of the acetomonoacetyl compound described above. Acetylation of 1-aceto-6-acetyldihydromorphine with acetic anhydride in pyridine gave an oily product which behaved similarly. It could be partially purified by slow distillation in a high vacuum at 140°; colorless glass.

Anal. Calc'd for $C_{22}H_{27}NO_6$: C, 66.8; H, 6.58.
Found: C, 66.3; H, 6.59.

1-Acetomorphine (XVII). To a solution of 1-aceto-3,6-diacetylmorphine (9 g.) in 20 ml. of normal hydrochloric acid was added 70 ml. of conc'd ammonia. The resinous white precipitate (sometimes fine crystals) went rapidly into solution; after 12 hours ammonia and water were removed at 40° under a vacuum until the separated crystals caused excessive bumping. It was recrystallized from alcohol-water (2:5), yield 6.7 g., 83%; turns brown at 245°, melts at 260–262.5° (evac. tube). It is very soluble in methanol and ethanol, slightly soluble in ethyl acetate, acetone or water; ferric chloride test intense blue-green. In alcohol, $(\alpha)_D^{20} -156°$ (*c*, 1.15).

Anal. Calc'd for $C_{19}H_{21}NO_4+H_2O$: C, 66.0; H, 6.71; H_2O, 5.2.
Found: C, 65.5; H, 7.04; loss at 100°, 5.2.

The *perchlorate* was prepared with 10% perchloric acid and purified from water; in alcohol, $(\alpha)_D^{20} -111°$ (*c*, 0.542); it melted at 261–262.5° decomp. (evac. tube).

Anal. Calc'd for $C_{19}H_{22}ClNO_8$: C, 53.3; H, 5.18.
Found: C, 53.4; H, 5.28.

The *hydrochloride* was prepared with alcoholic HCl and purified from 95% alcohol; m.p. 235–237° (evac. tube); in water, $(\alpha)_D^{20} -121°$ (*c*, 1.02).

Anal. Calc'd for $C_{19}H_{22}ClNO_4+0.5\ H_2O$: H_2O, 2.4.
Found: loss at 110°, 2.6.
Calc'd for $C_{19}H_{22}ClNO_4$: Cl, 9.7.
Found: Cl, 9.5.

1-Acetomorphine absorbed one mole of hydrogen (Pd-$BaSO_4$) but the product was a colorless glass which gave no crystalline derivatives.

1-Acetomorphine (XVII) *to 1-acetocodeine* (VI). A solution of 1-acetomorphine in methanol was added to excess ethereal diazomethane. The powdery precipitate dissolved with nitrogen evolution in about 2 hours. Removal of solvent left an oil, which crystallized with ethyl acetate; m.p. 149–150°, no depression in mixture with 1-acetocodeine.

SUMMARY

Acetylation of dihydromorphine and dihydrocodeine with sulfoacetic acid is described. The same nuclear acetylated compounds are obtained by hydrogenation of 1-acetomorphine and 1-acetocodeine derivatives. In the acetocodeine series, stepwise reduction of the nuclear acetyl group to the 1-hydroxyethyl and ethyl group can be accomplished.

1-Acetocodeine can be degraded to 1-aceto-α-methylmorphimethine, and this in turn converted to 1-aceto-β-methylmorphimethine, thus establishing the heretofore doubtful nature of the latter.

BETHESDA 14, MD.

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[Contribution from the Division of Physiology, National Institute of Health]

STUDIES IN THE ACRIDINE SERIES. III. DIALKYLAMINOALKYLAMINES DERIVED FROM 5- AND 7-Bz-METHOXY-9-CHLORO-1,2,3,4-TETRAHYDROACRIDINES[1]

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The preparation and properties of a series of 9-dialkylaminoalkylaminotetrahydroacridines were described in a recent paper from this laboratory (1), and it was shown that these substances were devoid of plasmodicidal activity. The presence of four additional hydrogen atoms on one of the benzenoid rings of tetrahydroacridine (I) apparently results in a system whose chemical demeanor is at once reminiscent of the acridines as well as of certain quinolines. The failure of the above-mentioned series of compounds to arrest—if only transiently—avian malarial infections (*P. gallinaceum*), may conceivably be attributed to the absence of those bz-substituents (*viz.*, chlorine and methoxyl) now known to be requisite for activity in the structurally analogous schizonticide Atabrine (2), on the one hand, and the various, reputedly active, substituted 4-aminoquinolines (3) on the other.

Insofar as the properties and reactivity of the *meso* function para to the heterocyclic nitrogen are concerned, the little-studied tetrahydroacridines (I) appear to be more closely related to the alkyl- or aryl-quinolines (II) than they are to acridine, the system upon which Atabrine is built (1). Variously substituted 4-aminoalkylquinolines of type IIa were the subject of recent, careful studies by Steck and his colleagues (4) who, unfortunately, gave no data regarding the activity of their compounds. Holcomb and Hamilton (5), as well as Van Arendonk and Shonle (6), in reexamining earlier work of Russian investigators (3), turned to 4-aminoalkylquinolines of type IIb which they reported to be slightly active. Gilman and Spatz (7) extended these ideas and introduced the novel "open-models" of Atabrine which were, in effect, arylquinolines of type IIc.

Exhaustive studies with Atabrine (2) have demonstrated that the effect of the methoxyl group upon antimalarial activity is virtually insignificant when compared with the contribution made by the chlorine atom. "Desmethoxyatabrine" was found to be nearly seven times as active as "deschloroatabrine" (2). On the other hand, less definite data are available relevant to the respective effects of the methoxyl group and the chlorine atom on the activity of alkyl substituted 4-aminoquinolines, though it appears that here, too, the influence of the chlorine atom is greater than that of the methoxyl group (3).

In continuing our studies with the 9-dialkylaminoalkylaminotetrahydroacridines, it was logical to extend these investigations to include bz-methoxyl- as well as bz-chloro- substituted tetrahydroacridines in order to ascertain the influence of these substituents on plasmodicidal activity. This communication concerns itself with the 5- and 7-bz-methoxy-9-aminotetrahydroacridines.

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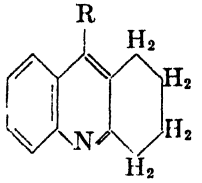
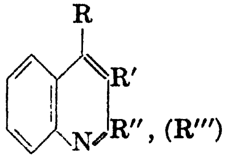
[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health. Communication XXIII in the series "Attempts to Find New Antimalarials."

The desired 5- and 7-methoxy-1,2,3,4-tetrahydroacridones were prepared by the method of Hughes and Lions (8). The latter investigators extended the Conrad and Limpach (9) synthesis of 4-hydroxyquinaldines, and prepared numerous tetrahydroacridones through condensation of the appropriate aniline with ethylcyclohexanone-2-carboxylate followed by cyclization of the resulting ethyl-2-arylamino-1-cyclohexene-1-carboxylates. The methoxytetrahydroacridones which we synthesized by this procedure were smoothly converted to the corresponding 9-chloro derivatives by treatment with phosphorus oxychloride. The condensations of the methoxy-9-chlorotetrahydroacridines with the various amines (Table I) were effected as recorded previously (1). It was found advantageous, however, to increase the reaction time from 24 to 60 hours (at 180°) to ensure better conversion to the desired product. Apart from the morpholino- and piperidino-substituted 7-methoxytetrahydroacridines, which were crystalline and could be sublimed unchanged in a high vacuum, the bulk of the reaction products were viscous oils. For the pharmacological tests, the latter were converted to the crystalline phosphates (solvated) since, in most cases, the hydrochlorides were not readily accessible. On the other hand, the perchlorates and picrates served best as analytical specimens, crystallizing solvent-free. The yields of the several methoxy-9-aminotetrahydroacridines dealt with in this investigation ranged from 40%, for the piperidino analog, to 95%, realized in the dibutylamino member of this series.



I. 9-Aminotetrahydroacridine
(R = Dialkylaminoalkylamine)



II. 4-Aminoquinoline
(R = Dialkylaminoalkylamine)
a) R′ = CH_3
b) R″ = CH_3
c) R‴ = 3-Chlorophenyl

Acknowledgment. The amines employed in this investigation were made available to us by Dr. R. C. Elderfield (Columbia Univ.) and Dr. Nathan Drake (Univ. of Maryland). Dr. George H. Coleman (State Univ. of Iowa) supplied the ethylcyclohexanone-2-carboxylate. The micro-analytical data are by C. A. Kinser and Betty Mount.

EXPERIMENTAL

Melting points are uncorrected. The experimental details given below are representative of the methods used in this investigation.

TABLE I

METHOXYDIALKYLAMINOALKYLAMINOTETRAHYDROACRIDINES

S.N.*	COMPOUND	APPEARANCE	FORMULA	M.P., C°.	ANALYSES			
					Calc'd		Found	
					C	H	C	H
14,015	5-CH$_3$O-9-(γ-di-*n*-butylaminopropylamino) 2HClO$_4$	Rect. plates[a]	$C_{25}H_{41}Cl_2N_3O_9$	189–191	50.2	6.91	50.2	6.82
X	5-CH$_3$O-9-(γ-di-*n*-amylaminopropylamino) 2C$_6$H$_3$N$_3$O$_7$	Yellow prisms[a]	$C_{39}H_{49}N_9O_{15}$	158–159.5	53.0	5 59	52.7	5.49
X	5-CH$_3$O-9-(γ-diisoamylaminopropylamino) 2HClO$_4$	Yellow needles[b]	$C_{27}H_{45}Cl_2N_3O_9$	169–171	51.7	7.24	51.6	7.33
—	5-CH$_3$O-9-(γ-diisoamylaminopropylamino) 2C$_6$H$_3$N$_3$O$_7$	Yellow prisms[a]	$C_{39}H_{49}N_9O_{15}$	164–165.5	53.0	5.59	52.9	5 89
13,915	7-CH$_3$O-9-(γ-dimethylaminopropylamino) 2HClO$_4$	White needles[c]	$C_{19}H_{29}Cl_2N_3O_9$	243–244	44.4	5.68	44.6	5.72
13,670	7-CH$_3$O-9-(γ-diethylaminopropylamino) 2C$_6$H$_3$N$_3$O$_7$	Pointed leaves[a]	$C_{33}H_{37}N_9O_{15}$	208–210	49.6	4.66	49.7	4.75
14,013	7-CH$_3$O-9-(γ-di-*n*-butylaminopropylamino) 2HClO$_4$	White needles[a]	$C_{25}H_{41}Cl_2N_3O_9$	196–198	50.2	6.91	50.2	7.23
14,012	7-CH$_3$O-9-(γ-di-*n*-amylaminopropylamino) 2HClO$_4$	Silky needles[a]	$C_{27}H_{45}Cl_2N_3O_9$	133–135	51.8	7.24	51.9	6.86
13,916	7-CH$_3$O-9-(γ-diisoamylaminopropylamino) 2HClO$_4$	White needles[a]	$C_{27}H_{45}Cl_2N_3O_9$	166–168	51.7	7.24	51.7	7.12
—	7-CH$_3$O-9-(morpholino) free base	White prisms[d]	$C_{18}H_{22}N_2O_2$	146–147.5	72.5	7.43	72.6	7.44
X	7-CH$_3$O-9-(morpholino) HCl	Yellow prisms[e]	$C_{18}H_{23}ClN_2O_2$	259–260 d.	64.6	6.92	64.7	7.09
—	7-CH$_3$O-9-(morpholino) HClO$_4$	Yellow prisms[f]	$C_{18}H_{23}ClN_2O_6$	264–265 d.	54.2	5.81	54.5	6.07
X	7-CH$_3$O-9-(piperidino) free base	White prisms[d]	$C_{19}H_{24}N_2O$	113.5–115	76 9	8.16	76.8	8.07
—	7-CH$_3$O-9-(piperidino) HClO$_4$	Yellow needles[c]	$C_{19}H_{25}ClN_2O_5$	261–263 d.	57.5	6.35	57.3	6 21

* The Survey Numbers (SN) are the identification numbers assigned by the Malaria Survey Office of the National Research Council. Those compounds designated by (X) were prepared subsequent to the dissolution of the Survey Office.

[a] Acetone + Ether; [b] Absol. alc. + Ether; [c] Absol. alc.; [d] sublimed; [e] 95% alc. + Ether; [f] 95% alc. ($C_6H_3N_3O_7$ = picric acid).

7-Methoxy-9-chloro-1,2,3,4-tetrahydroacridine. Ethyl cyclohexanone-2-carboxylate (61 g.) and *p*-anisidine (44 g.) condensed rapidly without catalyst, and the water formed was removed at 100° under diminished pressure. The powdered material was cyclized in 500 ml. of heavy liquid petrolatum at 285°, yield 68 g. (83% over-all). The crude acridone was added slowly to 200 ml. of phosphorus oxychloride at 100°, and refluxed for 30 min. This was decomposed with ice, and stirred into solution at room temp. The hydrochloride crystallized rapidly, and was washed with cold 3 *N* HCl. It was dissolved in one liter of hot water, decolorized, and precipitated crystalline while still warm, with 3 *N* ammonia; recrystallized from 250 ml. of alcohol, hard white crystals, m.p. 123–123.5°, photosensitive; yield 62 g. (85%).

Anal. Calc'd for $C_{14}H_{14}ClNO$: C, 67.9; H, 5.70.
Found: C, 68.2; H, 5.58.

5-Methoxy-9-chloro-1,2,3,4-tetrahydroacridine. Three-tenths mole (51 g.) of ethyl cyclohexanone-2-carboxylate and 0.3 mole (37 g.) of *o*-anisidine were condensed (5 drops of 6*N* HCl necessary) and the product cyclized as above, yield 38 g. (55%); from 500 ml. of alcohol, 22.5 g. (33%). This was added cold to 60 ml. of $POCl_3$, refluxed for 30 min., and poured on ice; the crystals slowly dissolved, and the base was precipitated with ammonia, 22.5 g. It was recrystallized twice from 40 ml. of methanol, removing a little inorganic material; 19.6 g. (81%), yellow needles, m.p. 128–128.5°.

Anal. Calc'd for $C_{14}H_{14}ClNO$: C, 67.9; H, 5.70.
Found: C, 67.9; H, 5.88.

7-Methoxy-9(γ-di-n-butylaminopropylamino)-1,2,3,4-tetrahydroacridine phosphate. Condensation of 6 g. of 7-methoxy-9-chloro-1,2,3,4-tetrahydroacridine with 9 g. (2 moles) of 3-di-*n*-butylaminopropylamine and a little copper-bronze powder was effected in a sealed tube heated at 180° for 60 hrs. The light brown, partially crystalline reaction product was worked up in the manner set forth in an earlier paper (1), and yielded 9.6 g. (95%) of a dark yellow syrup which was converted to the crystalline phosphate by treating, at 0°, with 25% alcoholic H_3PO_4 to Congo acidity. Recrystallization of the crude, solvated salt (12 g.) from methanol (Norit), gave 7 g. of colorless, needle-rosettes, m.p. 222–224° d.

As a rule, the perchlorates of the various reaction products were prepared with 25% alcoholic $HClO_4$; alcoholic picric acid (5%) served in the preparation of the picrates.

SUMMARY

Seven 7-methoxy-, and three 5-methoxy-9-dialkylaminoalkylaminotetrahydroacridines, as well as the intermediate 7- and 5-methoxytetrahydroacridones have been prepared. Antimalarial activity towards *P. gallinaceum* (chick infection) was absent in both series of drugs.

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[Contribution from the Division of Physiology,
National Institute of Health]

STUDIES IN THE ACRIDINE SERIES. IV. DIALKYLAMINOALKYLAMINES DERIVED FROM 5,9-, 6,9-, 7,9- and 8(?),9-DICHLORO-1,2,3,4-TETRAHYDROACRIDINES[1]

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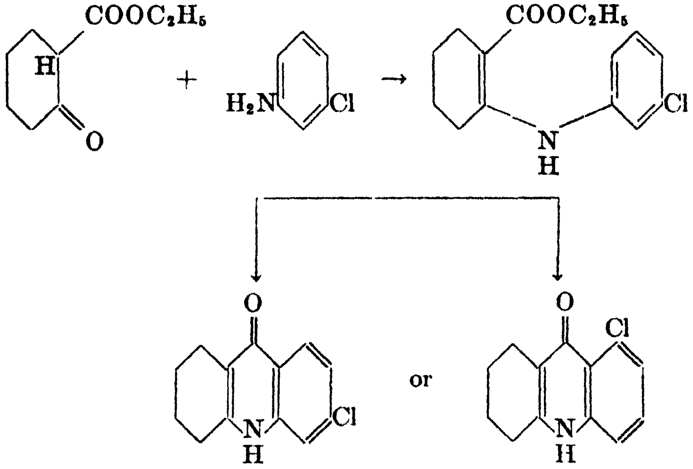
Received March 10, 1947

The preceding paper in this series (1) dealt with certain bz-methoxyl-substituted 9-dialkylaminoalkylaminotetrahydroacridines in which antimalarial activity was found lacking. The striking dissimilarity in the relative influence of methoxyl and of chlorine on plasmodicidal action has already been referred to in the case of Atabrine analogs (1). Disparate effects of these substituents also have been noted in connection with certain substituted 4-aminoquinolines where it was found that the chloro analogs were superior to those containing methoxyl groups (1). In the light of these considerations, the present investigation was designed to study the effect of bz-chloro-substitution on the activity of the 9-aminotetrahydroacridines.

The requisite 5- and 7-chlorotetrahydroacridones were synthesized by employing Hughes and Lions' extension of the Conrad and Limpach Synthesis (2), ethylcyclohexanone-2-carboxylate as well as *o*-chloro- and *p*-chloro-aniline respectively serving as starting materials. The resulting chlorotetrahydroacridones were converted to the corresponding dichlorotetrahydroacridines with phosphorus



6-Chlorotetrahydroacridone

8-Chlorotetrahydroacridone

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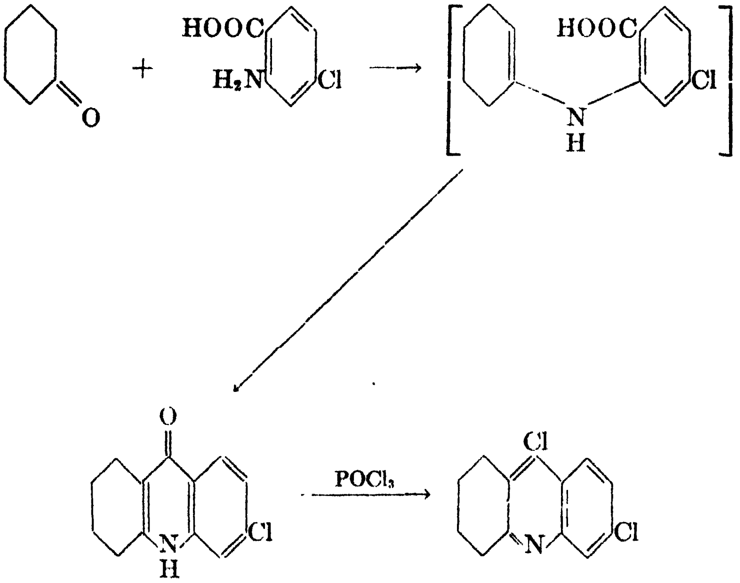
[1] This work was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Institute of Health. Communication XXIV in the series "Attempts to Find New Antimalarials."

oxychloride as described before (1). In the initial experiments dealing with 6-chlorotetrahydroacridone, ethylcyclohexanone-2-carboxylate was condensed with *m*-chloraniline and the product cyclized; a mixture of isomeric chlorotetrahydroacridones resulted. The accompanying diagram indicates how the isomers might arise. Separation of the isomeric chlorotetrahydroacridones or the corresponding dichlorotetrahydroacridines (produced by treating the acridones with phosphorus oxychloride) was not feasible owing to the nearly identical solubilities of the respective components. A separation was ultimately achieved, however, by taking advantage of the different solubilities of the phosphates of the amines obtained by condensing the dichloroacridine mixture with any of several dialkylaminoalkylamines. It was surprising to find that the isomers occurred in approximately equal amounts. In every case examined, the less soluble phosphate (designated isomer A) proved to be the 6-chloro isomer as will be demonstrated below. By inference, then, the more soluble phosphate (isomer B) should be the 8-chloro isomer, though this was not established conclusively. The identity of the 6-chloro-9-aminotetrahydroacridines was demonstrated by direct comparison of at least two salts of the amines, other than phosphate (*viz.*, perchlorate and picrate), with the corresponding salts of the amine derived from an authentic sample of 6,9-dichlorotetrahydroacridine. The latter was synthesized from cyclohexanone and 4-chloroanthranilic acid using Tiedtke's method (3), and proved to be quite homogeneous. It is evident from the equations below that only the 6-chloro isomer should result in this condensation.



6-Chlorotetrahydro-acridone

6, 9-Dichlorotetra-hydroacridine

TABLE I

CHLORODIALKYLAMINOALKYLAMINOTETRAHYDROACRIDINES

SN*	COMPOUND	APPEARANCE	FORMULA	M.P., °C.	ANALYSES			
					Calc'd		Found	
					C	H	C	H
—	5-Cl-9-(morpholino) free base	White prisms^{d}	$C_{17}H_{19}ClN_2O$	203–204.5	67.4	6.33	67.4	6.23
X	5-Cl-9-(morpholino) HCl	Yellow plates^{e}	$C_{17}H_{20}Cl_2N_2O$	215–216	60 2	5.94	59.9	6.00
X	5-Cl-9-(γ-dimethylaminopropylamino) $2C_6H_3N_3O_7$	Rhomb. prisms^{c}	$C_{30}H_{30}ClN_9O_{14}$	188–189	46.4	3.90	46.9	4.28
X	5-Cl-9-(γ-diethylaminopropylamino) $2C_6H_3N_3O_7$	Yellow prisms^{a}	$C_{32}H_{34}ClN_9O_{14}$	176–178	47.8	4.26	48.3	4.62
X	5-Cl-9-(γ-di-*n*-butylaminopropylamino) $2C_6H_3N_3O_7$	Rect. prisms^{c}	$C_{36}H_{42}ClN_9O_{14}$	162–163.5	50.3	4.92	50.4	5.14
—	6-Cl-9-(morpholino) free base	White prisms^{d}	$C_{17}H_{19}ClN_2O$	140–141	67.4	6.33	67.3	6.49
X	6-Cl-9-(morpholino) HCl	Yellow needles^{g}	$C_{17}H_{20}Cl_2N_2O$	267–268.5	60.2	5.94	60.1	5.92
X	6-Cl-9-(γ-dimethylaminopropylamino) free base	White prisms^{b}	$C_{18}H_{24}ClN_3$	105–106.5	68.0	7.61	68.4	7.49
—	6-Cl-9-(γ-dimethylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{18}H_{26}Cl_3N_3O_8$	220–221	41.7	5.05	41.4	4.98
12,983	6-Cl-9-(γ-diethylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{20}H_{30}Cl_3N_3O_8$	215–216.5	43.9	5.53	43.8	5.35
13,156	6-Cl-9-(γ-di-*n*-butylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{24}H_{38}Cl_3N_3O_8$	244–245	47.8	6.35	48.3	6.49
—	6-Cl-9-(γ-di-*n*-butylaminopropylamino) $2C_6H_3N_3O_7$	Yellow prisms^{c}	$C_{36}H_{42}ClN_9O_{14}$	210–211.5	50.3	4.92	50.2	4.97
12,985	6-Cl-9-(γ-di-*n*-amylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{26}H_{42}Cl_3N_3O_8$	203–205	49.5	6.71	49.7	6.89
13,157	6-Cl-9-(γ-diisoamylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{26}H_{42}Cl_3N_3O_8$	230–231	49.5	6.71	49.4	6.42
—	6-Cl-9-(γ-diisoamylaminopropylamino) $2C_6H_3N_3O_7$	Yellow prisms^{c}	$C_{35}H_{46}ClN_9O_{14}$	187–189	51.4	5.22	51.5	5.16
—	7-Cl-9-(morpholino) free base	White prisms^{d}	$C_{17}H_{19}ClN_2O$	165.5–167	67.4	6.33	67.7	6.55
X	7-Cl-9-(morpholino) HCl	Yellow prisms^{e}	$C_{17}H_{20}Cl_2N_2O$	251–252	60.2	5.94	60.3	6.03
X	7-Cl-9-(piperidino) $HClO_4$	Yellow needles^{f}	$C_{18}H_{22}Cl_2N_2O_4$	258–259	53.9	5.53	54.2	5.64
X	7-Cl-9-(γ-dimethylaminopropylamino) $2C_6H_3N_3O_7$	Yellow needles^{c}	$C_{30}H_{30}ClN_9O_{14}$	226.5–228	46.4	3.90	46.8	4.18
14,484	7-Cl-9-(γ-diethylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{20}H_{30}Cl_3N_3O_8$	243–244.5	43.9	5.53	44.2	5.70
13,923	7-Cl-9-(γ-di-*n*-butylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{24}H_{38}Cl_3N_3O_8$	181–182.5	47.8	6.35	47.6	6.47
13,924	7-Cl-9-(γ-di-*n*-amylaminopropylamino) $2C_6H_3N_3O_7$	Yellow needles^{c}	$C_{35}H_{46}ClN_9O_{14}$	179–181	51.4	5.22	51.5	5.32
X	7-Cl-9-(γ-diisoamylaminopropylamino) $2C_6H_3N_3O_7$	Yellow prisms^{a}	$C_{38}H_{46}ClN_9O_{14}$	172–174	51.4	5.22	51.5	5.42
X	8(?)-Cl-9-(γ-dimethylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{18}H_{26}Cl_3N_3O_8$	200–202	41.7	5.05	41.9	5.07
X	8(?)-Cl-9-(γ-diethylaminopropylamino) $2HClO_4$	Slender prisms^{a}	$C_{20}H_{30}Cl_3N_3O_8$	201–202.5	43.9	5.53	44.0	5.45
13,492	8(?)-Cl-9-(γ-di-*n*-butylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{24}H_{38}Cl_3N_3O_8$	191–192.5	47.8	6.35	47.9	6.18
13,667	8(?)-Cl-9-(γ-diisoamylaminopropylamino) $2HClO_4$	White needles^{a}	$C_{26}H_{42}Cl_3N_3O_8$	162–163.5	49.5	6.71	49.5	6.65

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* The Survey Numbers (SN) are the identification numbers assigned by the Malaria Survey Office of the National Research Council. Those compounds designated by (X) were prepared subsequent to the dissolution of the Survey Office. [a] Acetone + ether. [b] Ether + 30–60° pet. ether. [c] Acetone. [d] Sublimed. [e] 95% alc. + ether. [f] Absol. alc. + ether. [g] Absol. alc.; ($C_6H_3N_3O_7$ = picric acid).

The respective dichlorotetrahydroacridines were condensed with several amines (Table I) as described in an earlier communication (4). In accordance with the findings recorded in the preceding paper (1), a reaction time of 60 hours (at 180°) was found to be desirable for optimum conversion. Similarly, in virtually all cases, the reaction products were converted to, and tested in the form of, the crystalline phosphates (solvated). The solvent-free picrates and perchlorates were well suited for analytical data. The yields of the various chloro-9-aminotetrahydroacridines, with one exception, were 60% or higher; the piperidino analog was obtained in 40% yield.

Acknowledgment. We wish to thank Dr. R. C. Elderfield (Columbia Univ.) as well as Dr. Nathan Drake (Univ. of Maryland) for the various amines used in this work. We are indebted to Dr. George H. Coleman (State Univ. of Iowa) for the preparation of ethylcyclohexanone-2-carboxylate. Microanalyses are by C. A. Kinser and Betty Mount.

EXPERIMENTAL

Melting points are uncorrected. Experimental conditions, representative of those employed in this work, are given below.

5,9-Dichloro-1,2,3,4-tetrahydroacridine. 5-Chloro-1,2,3,4-tetrahydroacridone was prepared by the procedure of Hughes and Lions (2) from 0.5 mole (85 g.) of ethylcyclohexanone-2-carboxylate and 0.5 mole (64 g.) of *o*-chloroaniline; yield after purification from alcohol 58 g. (52%). This was added to 200 ml. of phosphorus oxychloride, refluxed for an hour, and decomposed with ice. From the decolorized solution ammonia precipitated a slime which was taken up in chloroform. The residue from this was crystallized twice from 500 ml. of methanol, separating from a small amount of sparingly soluble yellow needles of m.p. 136°. The main product melted at 89.5–90°, yellow needles; yield 35 g. (55%).

Anal. Calc'd for $C_{13}H_{11}Cl_2N$: C, 61.9; H, 4.40.
Found: C, 62.0; H, 4.51.

6-Chloro-1,2,3,4-tetrahydroacridone. Cyclohexanone (75 ml.) and 4-chloroanthranilic acid (50 g.) were condensed according to the Tiedtke (3) procedure at bath temperature 215° for one hour; 7.5 ml. of water was collected (calc'd 10 ml.). The acridone was triturated well with alcohol and sucked dry; yield 27 g. (40%). It was purified from alcohol for analysis, m.p. 340–345° with sublimation (evac. tube).

Anal. Calc'd for $C_{13}H_{12}ClNO$: C, 66.8; H, 5.18.
Found: C, 66.5; H, 5.25.

6,9-Dichloro-1,2,3,4-tetrahydroacridine. Twenty-seven grams of crude 6-chlorotetrahydroacridone was refluxed 45 min. with 130 ml. of $POCl_3$. The green suspension resulting from ice-decomposition was diluted to 2 liters, warmed on the steam-bath and filtered from flocculent material. Precipitation with ammonia and extraction into chloroform (clarified with Norit) gave a crystalline residue, recrystallized twice from methanol, large pale yellow prisms, 20 g. (68%), m.p. 86.5–87°; in mixture with the 5,9-dichloro isomer, 57–62°.

Anal. Calc'd for $C_{13}H_{11}Cl_2N$ · C, 61.9; H, 4.40.
Found C, 61.9; H, 4.55.

Ethyl 2 (p-chloroanilino)-1-cyclohexene-1-carboxylate. Ethyl cyclohexanone-2-carboxylate (0.5 mole) and *p*-chloroaniline (0.5 mole) were condensed by the Hughes and Lions' method, except that no catalyst was necessary. A small sample was purified from methanol for analysis; white crystals, m.p. 69.5–71°.

Anal. Calc'd for $C_{15}H_{18}ClNO_2$: C, 64.4; H, 6.47.
Found · C, 64.4; H, 6.63.

7,9-Dichloro-1,2,3,4-tetrahydroacridine. The crude product from the above condensation was freed of water at 100° in a vacuum and cyclized in 550 ml. of heavy liquid petrolatum at 285° until alcohol evolution ceased (*ca.* 5 min.). Trituration with ligroin and boiling alcohol gave 81 g. (69% over-all) of the acridone (2). This was refluxed 45 min. with 250 ml. of $POCl_3$ and worked up like the 5,9-dichloro isomer; it could be precipitated crystalline from the acid aqueous solution. It was recrystallized from 800 ml. of methanol, pale yellow crystals, 71 g. (81%). It melts at 84.5°; in mixture with the 5,9-isomer, m.p. 60–63°; with the 6,9-isomer m.p. 48–56°. It is a mild skin irritant.

Anal. Calc'd for $C_{13}H_{11}Cl_2N$: C, 61.9; H, 4.40.
Found: C, 62.0; H, 4.43.

Ethyl 2-(3-chloro-4-methoxyanilino)-1-cyclohexene-1-carboxylate. Condensation of equivalent amounts of 3-chloro-4-methoxyaniline and ethyl cyclohexanone-2-carboxylate in the presence of a few drops of 6 *N* HCl gave this derivative in good yield, purified from methanol, m.p. 87°.

Anal. Calc'd for $C_{16}H_{20}ClNO_3$: C, 62.0; H, 6.49.
Found: C, 61.9; H, 6.62.

Cyclization gave a product which was obviously a mixture of the two possible disubstituted tetrahydroacridones, and was not investigated further.

TABLE II

PERCHLORATES, M.P., °C.

	ISOMER A*	TRUE 6-CHLORO*	ISOMER B
Dimethylamino-	220–221	219–220	200–202
Di-*n*-butylamino-	245–246	244–245	191–193
Di-*n*-amylamino-	203–205	204–205.5	123–125
Diisoamylamino-	230–231	229–230.5	162–164
PICRATES, M.P., °C.			
Di-*n*-butylamino-	210–211 d.	208–210 d.	159–161
Diisoamylamino-	185.5–187 d.	185–187 d.	143–145

* No depression was observed in the mixture m.p.'s of these salts.

6,9- and 8(?),9-Dichlorotetrahydroacridines. Condensation of 0.5 mole of ethyl cyclohexanone-2-carboxylate and 0.5 mole of *m*-chloroaniline gave a mobile red oil, which was cyclized in the usual way, yield 84 g. (72%). Thirty grams of the mixture of isomers, refluxed 30 min. with $POCl_3$, gave after ice treatment and extraction into ether a pale brown oil, which crystallized from alcohol, 18.5 g. (57%), m.p. 61–65°.

5-Chloro-9-(γ-diethylaminopropylamino)-1,2,3,4-tetrahydroacridine dihydrochloride. A mixture of 5 g. of 5,9-dichloro-1,2,3,4-tetrahydroacridine, 5.3 g. (2 moles) of 3-diethylaminopropylamine, and a few mg. of copper-bronze powder was heated at 180° (sealed tube) for 63 hrs. The waxy, amber-colored product was suspended in water and extracted with ether. After removing a small amount of unreacted diethylaminopropylamine by fracttional extraction with dilute acetic acid as described in the first paper of this series (4), the dried (sodium sulfate) ether solution was concentrated *in vacuo*, and yielded 5.5 g. (77%) of a light, amber syrup. The latter gave 5.2 g. of crude dihydrochloride when treated in a cooled acetone solution with anhydrous hydrogen chloride. Recrystallization of the salt from absolute ethanol-ether (Norit) afforded 4.2 g. of minute, colorless needles, m.p. 200–202°.

6- and 8-(?)-Chloro-9-(γ-di-n-butylaminopropylamino)-1,2,3,4-tetrahydroacridine phosphates. Seven and two-tenths grams of the mixture of isomeric 6,9- and 8(?),9-dichlorotetrahydroacridines was heated with 10.6 g. (2 moles) of 3-di-*n*-butylaminopropylamine and a little copper-bronze powder for 60 hrs. (sealed tube) at 180°. The light brown, semi-solid reaction product was suspended in water and thoroughly extracted with ether. Unchanged di-*n*-butylaminopropylamine was fractionally extracted from the ether solution with dilute acetic acid. The bulk of the reaction product resulting from concentration (*vacuo*) of the dried ethereal solution, consisted of 9.8 g.(90%) of a viscous, amber syrup. This was dissolved in 20 ml. of absolute ethanol, cooled in ice-water, and treated dropwise with 25% alcoholic H_3PO_4 to Congo acidity. It was necessary to add small, additional quantities of absolute ethanol from time to time (during acidification) to thin down the resulting colorless sludge. Finally, 200 ml. of dry ether was added and the slightly hygroscopic precipitate filtered and dried in a vacuum desiccator ($CaCl_2$). The yield was 15 g. (solvated).

The crude phosphate mixture was dissolved in 200 ml. of boiling methanol (Norit), filtered and concentrated to approximately half the original volume. On standing overnight (at 20°) there separated 5.9 g. of small, colorless prisms melting at 210–216° (foams) (Isomer A). Dilution of the methanolic filtrate with dry ether to light, permanent turbidity and keeping in the refrigerator for 24 hrs., afforded 6 g. of a practically colorless, crystalline powder, m.p. 180–184° (Isomer B). Recrystallization of the latter (methanol-ether) raised the m.p. to 183–186°. Small amounts of phosphates A and B were converted to their respective free bases (NH_4OH-ether). The perchlorates of each were prepared with alcoholic perchloric acid (25%) and recrystallized from acetone-ether. The picrates were formed with 5% alcoholic picric acid and were recrystallized from acetone-ether.

That the less soluble phosphate fractions (designated Isomer A) obtained in the various preparations are identical with the 6-chloro-9-aminotetrahydroacridines is evident from the data shown in Table II.

The various 7-chloro analogs were prepared as described under 5-chloro-9-(γ-diethylaminopropylamino)-1,2,3,4-tetrahydroacridine

SUMMARY

A series of twenty chloro-substituted 9-dialkylaminoalkylaminotetrahydroacridines, as well as several precursory compounds used in their preparation, are described. Moderate activity towards *P. Gallinaceum* (chick infection) was found present in SN 14,484, while SN 13,924 showed slight activity.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MONSANTO CHEMICAL CO.]

SUBSTITUTED IMIDAZOLES AND 2-IMIDAZOLINES

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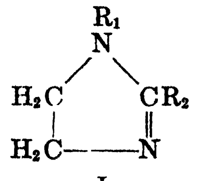
In the investigation of products for possible use against malaria, a number of 2-alkyl-substituted imidazoles (1) were found to have marked antimalarial activity[1] when tested against *Plasmodium lophurae* in ducklings. A number of 1,2-disubstituted 2-imidazolines (2) were found to have high *in vitro* activity against several bacteria, including *Streptococcus hemolyticus*, *Staphylococcus aureus*, *Pneumococcus* Type I, and *S. dysenteriae*. Related 2-alkyl-2-imidazolines of Formula Type I, where R_1 is hydrogen, were prepared and tested for comparison with the imidazoles which had antimalarial activity, and 1,2-disubstituted imidazoles of Formula Type II were made for comparison with the corresponding 2-imidazolines. The compounds were evaluated for chemotherapeutic and pharmacologic activity in The Lilly Research Laboratories.



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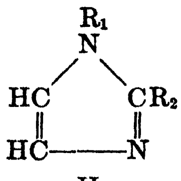

II

In the series of 2-alkylimidazoles prepared to investigate the effect of chain length on antimalarial activity, the most effective compound was found to be 2-tridecylimidazole, while 2-tetradecylimidazole was only slightly less active. The activity dropped markedly when the length of the alkyl chain was increased or decreased, 2-pentadecylimidazole being almost inactive, while 2-dodecylimidazole was fairly active and 2-hendecylimidazole (3) was slightly active. Although the most active compound sharply reduced the number of infecting organisms in the blood stream, it did not completely eliminate them. The corresponding 2-imidazolines, as well as the 1,2-dialkylimidazoles and the 1,2-dialkyl-2-imidazolines were devoid of any significant antimalarial activity.

Seven products, all 2-imidazolines, were found to be active *in vitro* against the *Streptococcus*, *Staphylococcus*, and *Pneumococcus*. When the 2-substituent was methyl, active compounds were obtained when decyl, dodecyl, or tetradecyl was introduced into the 1-position. 2-Imidazolines having a 2-hendecyl group were active when the 1-substituent was hydrogen, methyl, ethyl, or amyl. The entire series of compounds required to exhaust all the possible derivatives in the molecular weight range giving active products was not completed, but the data indicate that if one substituent is a short alkyl chain, the other must be in the range of C_{10} to C_{14}.

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[1] Antimalarial activities of some of these compounds are tabulated in the monograph, "A Survey of Antimalarial Drugs, 1941–1945," F. Y. Wiselogle, Editor; Edwards, Ann Arbor, 1946.

Four products had appreciable *in vitro* activity against *S. dysenteriae.* They were 1-decyl-2-methyl-2-imidazoline, 1-dodecyl-2-methylimidazole (4), 2-hendecyl-2-imidazoline, and 1-methyl-2-hendecyl-2-imidazoline.

Several compounds showed some activity against only one of the test organisms.

Ten compounds were found to possess mild to prolonged local anesthetic activity when applied to the cornea of a rabbit's eye. Three were imidazoles: 1-decyl-2-methyl-, 2-hendecyl-, and 1-methyl-2-hendecyl- (5), while the following 2-imidazolines were active:
1-decyl-2-methyl-, 1-dodecyl-2-methyl-, 1-methyl-2-nonyl-, 2-hendecyl-, 1-methyl-2-hendecyl-, 1-amyl-2-hendecyl-, and 2-(3-cyclohexylpropyl)-.

The introduction of benzyl, 3-phenylpropyl, and 3-cyclohexylpropyl groups into the 2-position of the imidazoles and 2-imidazolines produced compounds with no antimalarial or bactericidal activity.

Several of the 2-alkyl-2-imidazolines were found to be active insecticides. For example, 2-tridecyl-2-imidazoline is highly toxic to the red spider, *Tetranychus telarius* Linné. The activity of 2-alkyl-2-imidazolines as foliage fungicides has been reported recently by several workers (6, 7).

Numerous references have appeared in the literature showing many imidazolines and imidazoles to have marked pharmacological activity. Hartmann and Isler (8) tested a large number of 2-imidazolines and found that some were vasoconstrictors while others were vasodilators. An extensive report on derivatives with sympathomimetic activity was made by Scholz (9).

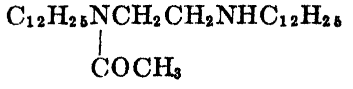
2-Alkyl-2-imidazolines were prepared by the reaction of esters with ethylenediamine to produce N-acylethylenediamines (10, 11, 12) which were not isolated but were cyclized directly by heating alone or with calcium oxide (11). In each of the acylation reactions there were obtained small to appreciable quantities of N,N'-diacylethylenediamines which could be converted into the corresponding 2-alkyl-2-imidazolines by treatment with magnesium as described by Chitwood and Reid (13). The yields of 2-imidazolines reported were those obtained directly, without consideration of recovery from the N,N'-diacylethylenediamines, although in several cases this was successfully accomplished. The preparation of N-monoacylethylenediamines was not investigated, but the application of an efficient method, such as that described by Weiner (12), who obtained excellent yields of monoacyl derivatives by reaction of 70% ethylenediamine with methyl esters of carboxylic acids at 100°, would undoubtedly result in improved over-all yields of 2-imidazolines using the simplified process described below.

Certain monoacylethylenediamines tend to lose water readily on heating, as shown by Hill and Aspinall (11), who observed that many aromatic monoacylethylenediamines undergo dehydration and cyclization to the 2-imidazolines merely on distillation. In his extended studies Aspinall (14) found that N-caproylethylenediamine is converted slowly into 2-amyl-2-imidazoline on distillation at temperatures in the range of 110–135°, but he was able to prepare N-caproylethylenediamine in 80% yield by reaction of ethyl caproate with ethylenediamine at 100°. In our experience, it was found possible to obtain a 65% yield of 2-amyl-2-imidazoline by the simple expedient of refluxing a mixture of one mole of methyl caproate with 3 moles of 90–100% ethylenediamine for about six hours, followed by removal of the excess ethylenediamine and distillation of the residue at a temperature above 125°. Other, higher, 2-alkyl- and 2-substituted alkyl-2-imidazolines were prepared with equal facility. For example, reaction of ethyl dodecanoate with ethylenediamine at reflux for 6 hours produced 70% of distilled 2-hendecyl-2-imidazoline. The time required for the acylation of ethylenediamine with the ester could be estimated conveniently by performing the reaction in a flask fitted with a fractionating column and carefully distilling off the methanol or ethanol until no further alcohol was liberated.

There are several alternative methods for preparing 2-imidazolines, one of the better being the reaction of ethylenediamine, ethylenediamine hydrochloride, and a carboxylic acid at about 300°, as described by Waldmann and Chwala (15).

The 2-alkylimidazoles were produced by dehydrogenation of the corresponding 2-imidazolines (3) by heating with a nickel hydrogenation catalyst (16) in the liquid phase.

In our experiments on the alkylation of 2-imidazolines with alkyl halides (2, 17), the formation of considerable quantities of by-products was observed. The results generally checked those recorded very recently by King and McMillan (18), who, working with 2-methyl-2-imidazoline, showed that in addition to the expected alkylation product, the alkyl halide quaternary salt of the alkylated 2-methyl-2-imidazoline was produced. The quaternary salt was found by them to hydrolyze readily to the acetylethylenediamine. When one mole of dodecyl bromide reacted with two moles of 2-methyl-2-imidazoline in refluxing anhydrous benzene, followed by treatment with cold aqueous alkali, about 40% of 1-dodecyl-2-methyl-2-imidazoline was formed, and there was obtained as a by-product a substantial amount of N-acetyl-N,N′-didodecylethylenediamine (III), resulting from hydrolysis of the intermediate quaternary compound.



$$C_{12}H_{25}\underset{\overset{|}{COCH_3}}{N}CH_2CH_2NHC_{12}H_{25}$$

III

When the same reaction was performed using no precautions to exclude traces of water, the reaction of dodecyl bromide or dodecyl chloride with 2-methyl-2-imidazoline produced, in addition to the other two products, a quantity of N,N′-didodecylethylenediamine, isolated directly from the reaction mixture as the hydrate upon quenching with water. This observation suggests that some of the 2-methyl-2-imidazoline was hydrolyzed to N-acetylethylenediamine early in the reaction or that some of the 1-dodecyl-2-methyl-2-imidazoline was hydrolyzed to N-acetyl-N′-dodecylethylenediamine, probably followed by further hydrolysis of the respective acetyl derivatives to the corresponding ethylenediamines prior to dialkylation. The ready hydrolysis of 2-imidazolines would be expected since they are cyclic amidines and it is well known that amidines are susceptible to hydrolysis with water (19). The easy hydrolysis of 2-imidazolines has been demonstrated by experiment (20), and the catalyzing effect of acids in the hydrolysis of certain 2-imidazolines (21) and acid amides (22) is recorded. The conditions during the alkylation with an alkyl halide in the presence of water would provide hydrogen ions which could catalyze the several hydrolytic reactions. This interpretation of the occurrence of the N,N′-dialkylethylenediamine is preferred over another possible mechanism, namely, the hydrolysis of the quaternary compound to III and further hydrolysis of the latter to N,N′-didodecylethylenediamine, because it was found that III is extremely difficult to hydrolyze either by acid or by alkali. This checks the conclusion of King and McMillan who stated that the acetyl derivatives in which the acyl group is attached to a secondary nitrogen atom of an ethylenediamine are resistant to hydrolysis.

The formation of by-products was observed in the alkylation of all 2-imidazolines used, but only the by-products obtained in a few cases were purified and identified.

1,2-Dialkylimidazoles were obtained either by nickel dehydrogenation of the 1,2-dialkyl-2-imidazolines or by alkylation of the 2-alkylimidazoles with alkyl halides (23). In the case of 1-methylation and 1-ethylation, dimethyl sulfate and diethyl sulfate were used, respectively. By-products formed in the alkylation of the imidazoles or in the lower alkylations were not investigated.

EXPERIMENTAL

All melting points are corrected. The analyses were performed by Mrs. J. D. Nevins, Mrs. R. C. Schropp, and Miss G. Pranger of the Monsanto Analytical Laboratory.

General methods of preparation. The procedures used for the preparation of the 2-imidazoline derivatives described in Table I and the imidazole derivatives described in Table II were as follows:

Procedure A. An ester of the appropriate acid reacted with ethylenediamine followed by thermal cyclization of the N-acylethylenediamine.

Procedure B. Similar to procedure A, but cyclization was effected with calcium oxide.

Procedure C. The corresponding 2-substituted or 1,2-disubstituted 2-imidazoline was dehydrogenated by heating with a nickel catalyst in the liquid phase.

Procedure D. The appropriate 2-substituted 2-imidazoline (2 moles) was alkylated with one mole of an alkyl halide in the presence or absence of an organic solvent like toluene or butanol or with an alkyl sulfate in the presence of aqueous alkali.

Procedure E. The appropriate 2-substituted imidazole was alkylated with one mole of an alkyl halide or with an alkyl sulfate, without the use of a solvent in either case.

2-Amyl-2-imidazoline. (*Procedure A*). A mixture of 78.1 g. (0.6 mole) of methyl caproate and 55.9 g. (0.9 mole) of 96.8% ethylenediamine was stirred and heated at reflux for 8 hours. The excess ethylenediamine was recovered by distillation, a small head fraction was taken to 148° (33 mm.), and the main fraction was distilled slowly at 150—157° (35 mm.); yield 57–65%. On redistillation the 2-amyl-2-imidazoline boiled at 139–141° (17 mm.).

TABLE I

SUBSTITUTED 2-IMIDAZOLINES

R_1[a]	R_2[a]	PROCEDURE	YIELD	B P., °C.	MM. Hg	M.P., °C.	EMPIRICAL FORMULA	ANALYSIS[b] Calc'd	ANALYSIS[b] Found
			%					N	N
C_7H_{15}	CH_3[c]	D	69	107–109	2.5	Oil	$C_{11}H_{22}N_2$	15.4	15.8
$C_{10}H_{21}$	CH_3[d]	D	59	135–136	3	Oil	$C_{14}H_{28}N_2$	12.5	12.4
$C_{12}H_{25}$	CH_3[d]	D	38	161–162	2	Oil	$C_{16}H_{32}N_2$	11.1	11.1
$C_{14}H_{29}$	CH_3[d]	D	50	191–193	6	Oil	$C_{18}H_{36}N_2$	10.0	9.8
$C_6H_5CH_2$	CH_3	D	39	162–163	16	Oil	$C_{11}H_{14}N_2$	16.1	15.9
$C_{10}H_{21}$	C_5H_{11}[e, f]	D	43	164–166	1.5	Oil	$C_{18}H_{36}N_2$	10.0	10.0
$C_{12}H_{25}$	C_5H_{11}[d]	D	46	196–197	3	Oil	$C_{20}H_{40}N_2$	9.1	8.9
CH_3	C_7H_{15}[e]	D	33	93–96	2	Oil	$C_{11}H_{22}N_2$	15.4	14.9
CH_3	C_9H_{19}[e]	D	60	142–143	5	Oil	$C_{13}H_{26}N_2$	13.3	13.1
CH_3	$C_{11}H_{23}$[e, g]	D	41	167–172	6	Oil	$C_{15}H_{30}N_2$	11.8	11.9
C_2H_5	$C_{11}H_{23}$[g]	D	42	170–178	2.5	[h]	$C_{16}H_{32}N_2$	11.1	10.9
C_5H_{11}	$C_{11}H_{23}$[g]	D	61	172–173	2	Oil	$C_{19}H_{38}N_2$	9.5	9.2
H	$C_{12}H_{25}$[i]	A	57	163–165	3	87–88[j]	$C_{15}H_{30}N_2$	11.8	11.7
H	$C_{13}H_{27}$[k]	A	65	179–180	2	88–89[j]	$C_{16}H_{32}N_2$	11.1	11.0
H	$C_{13}H_{25}$[l]	B	66	207–218	13	[h]	$C_{16}H_{30}N_2$	11.2	10.9
H	$C_{14}H_{29}$	A	72	191–195	4	92–93[j]	$C_{17}H_{34}N_2$	10.5	10.4
H	$C_6H_5(CH_2)_3$	A	71	202–203	20	Oil	$C_{12}H_{16}N_2$	14.9	14.6
H	$C_6H_{11}(CH_2)_3$	A	73	159–160	5	[m]	$C_{12}H_{22}N_2$	14.4	14.5

[a] All alkyl radicals are normal.

[b] Determined by the Dumas combustion method.

[c] 2-Methyl-2-imidazoline used as an intermediate was described by Hill and Aspinall (11), and others. It was prepared by procedure B.

[d] Described in ref. (2).

[e] 2-Amyl-, 2-heptyl-, 2-nonyl-, and 2-hendecyl-2-imidazoline, used as intermediates, were described by Chitwood and Reid (13). They were prepared by procedure A.

[f] Described in ref. (4).

[g] Described in ref. (5).

[h] Waxy solid.

[i] 2-Dodecyl-2-imidazoline also was made from dodecyl cyanide by converting it to the imino ether which was reacted with ethylenediamine; yield, 70%.

[j] Recrystallized from methanol.

[k] 2-Tridecyl-2-imidazoline was mentioned by Waldmann and Chwala, U. S. Patent 2,215,862 (9-24-40), and described in ref. (1).

[l] 1-Tridecenyl.

[m] Solid. Can be recrystallized from ligroin.

Treatment of the still residue with magnesium (13) at 300° under 35 mm. absolute pressure produced additional product, raising the yield to well over 90%.

1-Amyl-2-hendecylimidazole. (*Procedure C*). A mixture of 37.1 g. of 1-amyl-2-hendecyl-2-imidazoline and 4.2 g. of 50% nickel-petroleum paste, in a flask equipped with a stirrer, thermometer, and reflux condenser connected to a bubble-counter, was stirred and heated. The evolution of hydrogen began at 210°. The batch temperature was raised gradually

TABLE II

SUBSTITUTED IMIDAZOLES

R_1[a]	R_2[a]	PROCEDURE	YIELD	B.P., °C.	MM. Hg	M.P., °C.	EMPIRICAL FORMULA	ANALYSIS[b]	
								Calc'd	Found
			%					N	N
C_7H_{15}	CH_3	C	89	118–122	2.5	Oil	$C_{11}H_{20}N_2$	15.5	15.6
$C_{10}H_{21}$	CH_3[c]	C	96	157–158	3	Oil	$C_{14}H_{26}N_2$	12.6	12.7
$C_{12}H_{25}$	CH_3[c]	C	93	164–166	3	Oil	$C_{16}H_{30}N_2$	11.2	11.4
$C_{14}H_{29}$	CH_3[c]	C	90	185–186	2	Oil	$C_{18}H_{34}N_2$	10.1	10.4
$C_{10}H_{21}$	C_5H_{11}[c]	C	94	175–176	2	Oil	$C_{18}H_{34}N_2$	10.1	9.8
$C_{12}H_{25}$	C_5H_{11}[c]	C	95	184–185	1	Oil	$C_{20}H_{38}N_2$	9.1	8.8
CH_3	C_7H_{15}	C	86	166–169	25	Oil	$C_{11}H_{20}N_2$	15.5	15.1
CH_3	C_9H_{19}	C	81	149–154	3.5	Oil	$C_{13}H_{24}N_2$	13.5	13.3
CH_3	$C_{11}H_{23}$[d]	E	39	134–167	3.5	Oil	$C_{15}H_{28}N_2$	11.9	11.6
		C	67	158–172	2.5	Oil		—	—
C_5H_{11}	$C_{11}H_{23}$[d]	E	55	218–219	10	Oil	$C_{19}H_{36}N_2$	9.6	9.8
		C	88	—	—	Oil		—	—
H	$C_{12}H_{25}$[e]	C	85	194–196	3	77–78[f]	$C_{15}H_{28}N_2$	11.9	12.3
H	$C_{13}H_{27}$[g]	C	89	208–210	1.5	81–82[f]	$C_{16}H_{30}N_2$	11.2	11.5
H	$C_{13}H_{25}$[h]	C	81	230–241	13	Paste	$C_{16}H_{28}N_2$	11.3	11.4
H	$C_{14}H_{29}$	C	81	219–221	3	83–84[f]	$C_{17}H_{32}N_2$	10.6	10.5
H	$C_{15}H_{31}$[i, j]	C	84	220–223	3.5	87–88[f]	$C_{18}H_{34}N_2$	10.1	10.0
H	$C_6H_5CH_2$[k]	C	92	201–202	12	125–126[l]	$C_{10}H_{10}N_2$	17.7	17.7
H	$C_6H_5(CH_2)_3$	C	77	194–195	2	90–91[f]	$C_{12}H_{14}N_2$	15.0	15.0
H	$C_6H_{11}(CH_2)_3$	C	85	190–195	7	78–79[m]	$C_{12}H_{20}N_2$	14.6	14.6

[a] All alkyl radicals are normal.

[b] Determined by the Dumas combustion method.

[c] Described in ref. (4).

[d] Described in ref. (5).

[e] 2-Dodecylimidazole was mentioned by name, but not further described, by Graenacher and Meyer (3).

[f] Recrystallized from methanol.

[g] Described in ref. (1).

[h] 1-Tridecenyl.

[i] 2-Pentadecyl-2-imidazoline, the intermediate, was described in French Patent 835,426 (12-21-38); *Chem. Zentr.*, **1939**, I, 3824. It was prepared by procedure B.

[j] 2-Pentadecylimidazole was mentioned by Waldmann and Chwala, French Patent 49,039 (10-14-38); *Chem. Zentr.*, **1939**, I, 286.

[k] 2-Benzyl-2-imidazoline, the intermediate, was described by Sonn (26), and by Aspinall (14). It was prepared by procedure A.

[l] Recrystallized from aqueous methanol. Sonn and Greif, *Ber.*, **66**, 1900 (1933), prepared 2-benzylimidazole by decarboxylation of 2-benzylimidazole-4,5-dicarboxylic acid, and reported m.p. 125–126°.

[m] Recrystallized from acetone.

to 245°, at which temperature dehydrogenation was essentially complete; the total reaction time was 20 minutes. Distillation directly from the catalyst yielded 3.5 g. of head fraction, b.p. 100–179° (5 mm.), and 25.6 g. (76.6%) of 1-amyl-2-hendecylimidazole, b.p. 170–180° (1.5 mm.).

Alkylation of 2-methyl-2-imidazoline with dodecyl bromide. (*Procedure D*). A mixture of 50.4 g. (0.6 mole) of 2-methyl-2-imidazoline, 74.7 g. (0.3 mole) of dodecyl bromide, and 100 cc. of benzene was refluxed for 7 hours and cooled to 25°. Water, 150 cc., and 24 g. of 50% sodium hydroxide solution were added, the mixture was stirred for one hour, and a colorless, waxy solid, dry weight, 15 g., was filtered from the mixture. This proved to be N,N'-didodecylethylenediamine hydrate, m.p. 71–72° (melt not entirely clear), after recrystallization from 95% ethanol.

Anal. Calc'd for $C_{26}H_{56}N_2 \cdot H_2O$: C, 75.3; H, 14.1; N, 6.8; H_2O, 4.3.
Found: C, 75.1; H, 14.0; N, 7.1; H_2O, 4.4.

The anhydrous base was obtained by distillation, b.p. 225–230° (1.5 mm.); f.p. 39.8°, with no further purification. Recently the m.p. 15–17° was reported in the literature (24) for N,N'-didodecylethylenediamine.

The dihydrochloride was prepared by treating an alcoholic solution of N,N'-didodecylethylenediamine hydrate with aqueous hydrochloric acid. After recrystallization from 95% ethanol, it sintered at about 272°.

Anal. Calc'd for $C_{26}H_{56}N_2 \cdot 2HCl$: Cl, 15.1. Found: Cl, 15.1.

The above salt apparently was identical with N,N'-didodecylethylenediamine dihydrochloride prepared from the pure base made by alkylation of ethylenediamine with dodecyl bromide, since a mixture with the authentic sample sintered at about 272°.

The benzene layer was separated from the filtrate obtained after removal of the waxy solid, and the products were distilled. Three fractions were collected. (a) 1-Dodecyl-2-methyl-2-imidazoline was obtained at 204–209° (13 mm.); yield, 30 g. (38%). Upon redistillation the product boiled at 158-159° (4 mm.). (b) An intermediate fraction, 8 g., was collected at 190–240° (4 mm.). (c) N-acetyl-N,N'-didodecylethylenediamine (III), 20 g., was collected at 243–250° (4 mm.).

Anal. Calc'd for $C_{28}H_{58}N_2O$ (III): C, 76.6; H, 13.3; N, 6.4.
Found: C, 76.6; H, 13.6; N, 6.3.

III was found to be highly resistant to hydrolysis with alkali or acid, but upon refluxing with aqueous-alcoholic hydrochloric acid for 15–20 hours, followed by cooling, crystals of N,N'-didodecylethylenediamine dihydrochloride, sintering point about 268°, were obtained. A mixture of this salt with the authentic sample did not show a depressed sintering point.

Anal. Calc'd for $C_{26}H_{56}N_2 \cdot 2HCl$: Cl, 15.1. Found: Cl, 15.1.

Virtually the same yield of 1-dodecyl-2-methyl-2-imidazoline was obtained when the alkylation was performed with dodecyl chloride. When strictly anhydrous reagents were used, no N,N'-didodecylethylenediamine was formed, but N-acetyl-N,N'-didodecylethylenediamine was isolated as before; the yield of alkylated 2-imidazoline, however, was not improved by using anhydrous conditions.

1-Ethyl-2-hendecyl-2-imidazoline. (*Procedure D*). Fifty grams of 2-hendecyl-2-imidazoline (13) (0.223 mole) was melted and the temperature maintained at 70–80° while 34.4 g. of diethyl sulfate (0.224 mole) and 8.9 g. of sodium hydroxide in 15 cc. of water were added slowly and simultaneously from separate burettes, keeping the reaction mixture just alkaline to phenolphthalein. After all the alkali and diethyl sulfate had been added, the mixture was heated for 2 hours at 80°, cooled to 25°, treated with 100 cc. of butanol and 40 g. of 50% aqueous sodium hydroxide solution, and stirred for one hour. The butanol layer was separated, washed twice with 50-cc. portions of water, the solvent was removed and the product distilled. A 19.7 g. forerun, taken at 142–172° (2.5 mm.), contained 13 g. of 2-hendecyl-2-imidazoline, isolated by redistillation. The 1-ethyl-2-hendecyl-2-imidazoline boiled at 170–178° (2.5 mm.); yield, 23.5 g. (42%).

1-Amyl-2-hendecyl-2-imidazoline. (*Procedure D*). A charge of 90 g. (0.4 mole) of 2-hendecyl-2-imidazoline (13), in a flask equipped with an agitator, thermometer and reflux condenser, was stirred and heated at 140–150°. Amyl chloride, 21.3 g. (0.2 mole), was added during about 30 minutes. The reaction mixture was held at about 150° for 16 hours and then cooled to 60°. Water, butanol, and 17 g. of 50% aqueous sodium hydroxide solution were added, the mixture was stirred for one hour at 30°, and the butanol layer was separated and fractionated. The head fraction, 7.2 g., boiled at 60–125° (5 mm.). The recovered 2-hendecyl-2-imidazoline was collected in the range 145–180° (5 mm.); weight, 43 g. Yield of 1-amyl-2-hendecyl-2-imidazoline, b.p. 180–200° (5.5 mm.), 41.5 g. (70%).

1-Amyl-2-hendecylimidazole. (Procedure E). A mixture of 20 g. (0.09 mole) of 2-hendecylimidazole (3) and 9.4 g. (0.09 mole) of amyl chloride in a flask equipped with an agitator, thermometer, and reflux condenser was stirred and heated at 125–150° for 3 hours, cooled to 30°, dissolved in 25 cc. of water, and treated with 10 g. of 50% aqueous sodium hydroxide solution. The solid that precipitated was filtered from the reaction mixture and washed with water; dry weight, 4 g. The oily product in the filtrate was taken up with benzene, the non-aqueous (upper) layer was separated and distilled. A small forerun boiling at 145–205° (10 mm.) was obtained; weight, 1.7 g. The 1-amyl-2-hendecylimidazole boiled at 218–219° (10 mm.); yield, 14.4 g. (55%).

Sebacic acid diimino ether. A mixture of 8.2 g. (0.05 mole) of sebaconitrile (25) and 4.6 g. (0.10 mole) of absolute alcohol was stirred and cooled in an ice-bath and dry hydrogen chloride was passed in until no more was absorbed. The mixture became thick, and in about an hour following the start of hydrogen chloride addition, it solidified. The crude diimino ether, 19.4 g., was a hygroscopic solid soluble in hot chloroform; m.p. 85–86° with evolution of gas. No loss in weight occurred when the product was placed under reduced pressure.

The reagents and apparatus used in this experiment must be strictly dry, or a large amount of sebacic acid diamide will be formed.

2,2′-Octamethylenedi-2-imidazoline. This compound was prepared by the general method described by Sonn (26). Crude sebacic acid diimino ether (19.4 g.) was dissolved in 50 cc. of chloroform by refluxing, the excess hydrogen chloride being driven off by this procedure. The solution was cooled to 30° and 6.0 g. (0.1 mole) of anhydrous ethylenediamine was added; a precipitate formed immediately, and some heat was evolved. The mixture was refluxed until no more ammonia gas was liberated, cooled to 25°, and the solid remaining was filtered off and washed with chloroform. The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in 50 cc. of water, and the solution was treated with 4.0 g. of aqueous 50% sodium hydroxide solution added dropwise. The colorless solid that precipitated was filtered off, washed with water, and dried at 70°; yield 8.8 g. (70%); m.p. 179–181°. On recrystallization from ethanol it was obtained as long prismatic needles, m.p. 185–187°.

This product was described in a French Patent (27), where it was made by heating a mixture of sebacic acid, ethylenediamine, and ethylenediamine hydrochloride, and in a U. S. Patent (28), where it was made by heating ethyleneurea with sebacic acid. The latter reference gives the m.p. as 185–187°.

1-Dodecyl-2-methylbenzimidazole. This product was made in 58% yield by reaction of two moles of 2-methylbenzimidazole (29) and one mole of dodecyl chloride in boiling xylene. A similar procedure was used in a patent (30), but the product was not described. It is a yellow liquid, b.p. 225–227° (5 mm.).

Anal. Calc'd for $C_{20}H_{32}N_2$: N, 9.3. Found: N, 9.3.

A number of 1,2-dialkylbenzimidazoles were made recently by Weidenhagen and coworkers (31).

Ethyl pentadecanoate. A mixture of 150 g. of 95% ethanol, 150 g. of concentrated sulfuric acid, and 68 g. of tetradecyl cyanide (0.305 mole) was agitated at reflux temperature for four hours. The reaction product was poured into 400 cc. of ice and water, and extracted with 100 cc. of ether and then with 100 cc. of benzene. The combined ether and benzene extracts were washed with water and dried. The solvent was removed, and the product distilled; b.p. 156–158° (5 mm.); yield, 69.3 g. (87%). A test of the method of Christmann (32), using hydrogen chloride, gave a 77% yield. The ester was used in the preparation of 2-tetradecyl-2-imidazoline.

Ethyl tridecanoate. This ester was obtained in 91% yield using dodecyl cyanide, ethanol and sulfuric acid in the process described above for ethyl pentadecanoate; b.p. 133–134°

(4 mm.). The process given in *Organic Syntheses* (33), is considerably more complicated, requiring hydrolysis of the nitrile, followed by forty-eight hours' esterification of the crude acid. The ester was used in the preparation of 2-dodecyl-2-imidazoline.

Ethyl 2-tetradecenoate. 2-Tetradecenoic acid was made by bromination of myristic acid (1, 34) followed by dehydrohalogenation with quinoline at 200°. The acid was esterified with absolute ethanol and sulfuric acid, yielding 62% of ester, b.p. 165–167° (11 mm.), which was used in the preparation of 2-(1′-tridecenyl)-2-imidazoline.

Methyl 4-cyclohexylbutyrate. This ester, required for the preparation of 2-(3′-cyclohexylpropyl)-2-imidazoline, was made in 75% yield by Dr. F. C. Meyer by hydrogenation of methyl 4-phenylbutyrate (35) without a solvent, using a nickel catalyst; b.p. 124° (24 mm.). Ethyl 5-cyclohexylvalerate was prepared in a similar manner by Baker and Dodson (36), who hydrogenated ethyl 5-phenylvalerate in alcohol solution using Raney nickel.

N,N′-Ditetradecylethylenediamine hydrate. This material was isolated as a by-product in the reaction of 2-methyl-2-imidazoline with tetradecyl chloride. Upon recrystallization from 95% ethanol, it was obtained in the form of white, waxy crystals, m.p. 72–73° (the melt was cloudy); Linsker and Evans (24) reported m.p. 24–26° for N,N′-ditetradecylethylenediamine.

Anal. Calc'd for $C_{30}H_{64}N_2 \cdot H_2O$: N, 6.0; H_2O, 3.8.
Found: N, 5.9; H_2O, 3.8.

SUMMARY

The preparation and properties of a number of substituted 2-imidazolines and imidazoles have been reported.

A simplified method of preparing 2-alkyl-2-imidazolines has been described.

The reaction of 2-alkyl-2-imidazolines with alkyl halides has been investigated and the products formed have been identified in several instances.

Many of the compounds described have activity in the biological field.

St. Louis 4, Mo.

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[Contribution from the Noyes Chemical Laboratory, University of Illinois and the Research Laboratory of Givaudan-Delawanna, Inc.]

THE STRUCTURE OF MUSK KETONE AND MUSK TIBETENE[1]

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M. S. CARPENTER

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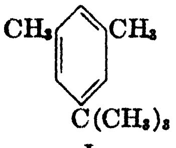
Chloromethylation of 5-*t*-butyl-1,3-dimethylbenzene (I) yields a single product which was identified by Carpenter (1) as 2-*t*-butyl-4,6-dimethylbenzyl chloride (II). The symmetrical structure (III), however, was assigned to this compound by Fuson, Denton, and Kneisley (2) and by Buu-Hoï and Cagniant (3). The evidence favored the unsymmetrical structure, since the hydrocarbon obtained by reduction had been prepared by treatment of pseudocumene with *t*-butyl chloride in the presence of aluminum chloride (4). Admittedly this is not strong evidence, since rearrangement of groups may have occurred in the presence of aluminum chloride. Moreover, the yields were low.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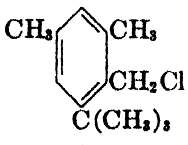
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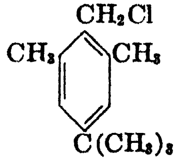
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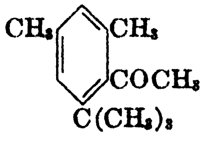
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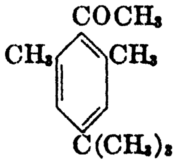
V

Carpenter's conclusion derived further support by analogy with the acetylation of the butylxylene by the Friedel-Crafts method; the acetylation product, mother substance of musk ketone, was believed to possess the unsymmetrical structure, IV (6, 10).

In a search for additional evidence relative to the structure of the chloromethylation product and the acetyl compound, we have carried out numerous experiments, many of which consisted in attempts to check earlier reports. The results have convinced us that these compounds have the symmetrical (III and V) rather than the unsymmetrical structures (II and IV). From this conclusion it follows that the structures hitherto assigned to musk ketone and Musk Tibetene are to be revised also and are correctly represented by formulas

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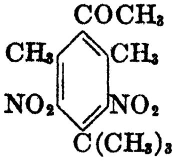
VI and VII, respectively. The conclusion with reference to musk ketone corroborates that of Chichibabin (9).



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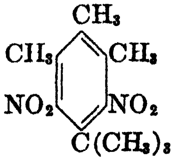
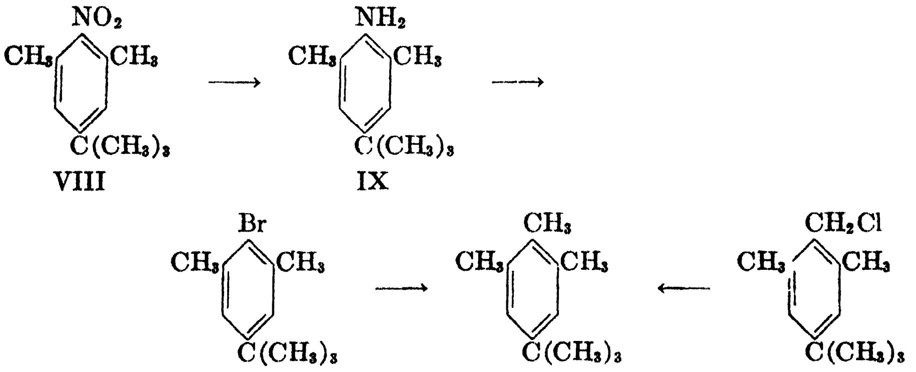


VII

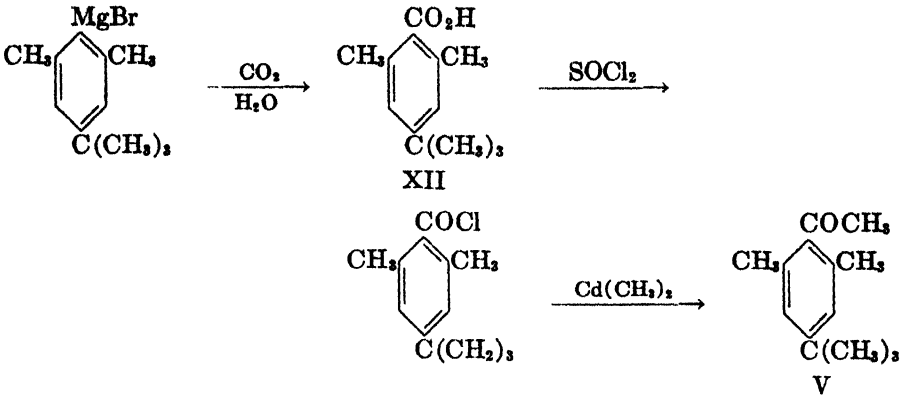
The primary reference compound in our work was the mononitration product (m.p. 85°) (VIII). Its structure was established by Baur (7, 10) by an unequivocal method and has never been questioned. We have converted it to the corresponding bromo derivative (X) by way of the amine (IX). The amine was made by reducing the nitro compound and was transformed to the bromo compound by the Sandmeyer method. The product, a solid of melting point 51°, is the same as that obtained by direct bromination of the hydrocarbon (8) or by heating the N,N-dibromo derivative of 4-*t*-butyl-2,6-dimethylbenzamide (9).



VIII IX X XI III

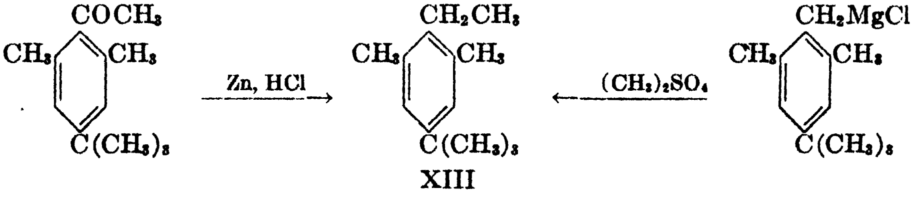
The bromo compound, the structure of which was thus made certain, was employed as the reference substance in the determination of the structure of the chloromethyl derivative. Treatment with zinc dust and water converted the chloromethyl compound to 5-*t*-butylhemimellitene (XI) (m.p. 32°), the structure of which was established by showing that the compound could be made also by the action of methyl sulfate on the Grignard reagent prepared from the bromo compound (X). The two samples of the butylhemimellitene were nitrated separately. The nitration products (m.p. 136°) proved to be identical and are undoubtedly Musk Tibetene (VII).

The bromo compound served also to establish the structure of musk ketone. Carbonation of the Grignard reagent made from the bromo derivative yielded an acid (XII), the acid chloride of which reacted with dimethylcadmium to yield a ketone (m.p. 46–47°) identical with that which is formed by the Friedel-Crafts method.

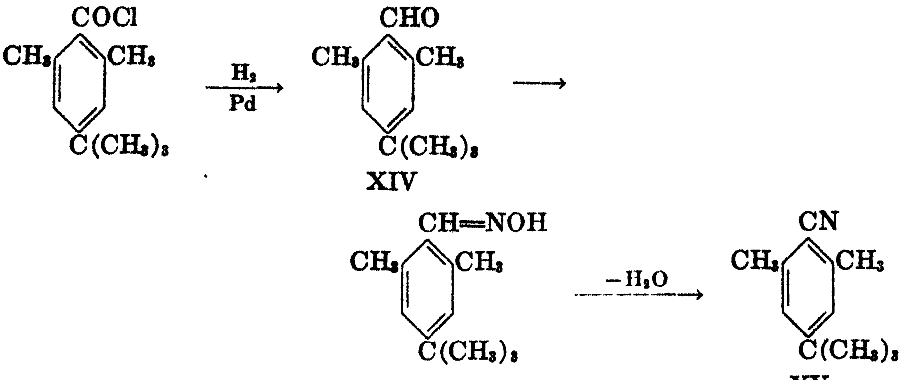


Its structure is, therefore, correctly represented by Formula V and that of musk ketone by Formula VI.

Although the foregoing proofs of structure for the chloromethyl compound (III) and for the acetyl derivative (V) involve only reactions which are known to proceed normally, the importance of the problem seemed to warrant additional confirmation. It has been found possible to relate the two key compounds through the hydrocarbon, 4-*t*-butyl-2,6-dimethylethylbenzene (XIII). It was obtained from the ketone by a Clemmensen reduction and by the action of dimethyl sulfate on the Grignard reagent derived from the chloromethyl compound. The two samples of the ethyl compound yielded the same dinitro derivative (m.p. 129°).



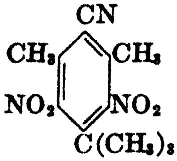
It remained to discover if possible the error in the original structure proof of Baur (10) which led him to assign the unsymmetrical structure to the methyl aryl ketone. The symmetrical nitrile (XV) appears to be the key compound in his proof. It has been prepared from the amine by the Sandmeyer method (10, 11) and was reported to melt at 88° (10). In one report (11) this melting point, possibly by a misprint, was given as 83°. We have prepared it from the amine by the Sandmeyer method and from the bromo compound by the Rosenmund-von Braun method. The two products had the same melting point (64.5–65.5°) and proved to be identical. We were able to relate this nitrile to the acid (and hence to the methyl ketone) through the aldehyde (XIV) obtained by reduction of the acid chloride. It may be mentioned in passing that a plan for preparing the aldehyde from the methyl ketone by an oxidative process was not carried beyond the glyoxal. Dehydration of the oxime of the aldehyde yielded a sample of the nitrile which was the same as the others.



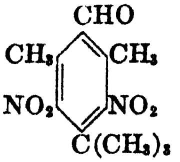
XIV

XV

The method for converting the aldehyde to the nitrile was that employed by Baur. Our aldehyde had the same melting point (60°) as his. Likewise the dinitro derivative of our sample had the melting point (111°) reported by Baur. Yet the nitrile which we obtained melted at 64.5–66.5° instead of 70°, the melting point reported by Baur. Thus we have made the nitrile in three different ways without observing either of the compounds reported by Baur. From these results it seems certain that musk cyanide (10, 11) and musk aldehyde (12) possess the symmetrical structures XVI and XVII, respectively. Chichibabin also came to the conclusion that musk aldehyde had the symmetrical structure (9).



XVI



XVII

EXPERIMENTAL

Nitration of 5-t-butyl-1,3-dimethylbenzene. The reaction, first reported by Baur (7), was carried out according to a procedure similar to that of Powell and Johnson for nitromesitylene (13). The symmetrical product, *4-t-butyl-2,6-dimethylnitrobenzene*, was obtained in 66% yield; m.p. 84–85°. The liquid isomer, *6-t-butyl-2,4-dimethylnitrobenzene*, was isolated from the filtrates in a yield of 29%; b.p. 109–110.5° (4 mm.); n_D^{20} 1.5145 d_{20}^{20} 1.0373. Molecular refractivity; Calc'd for $C_{12}H_{17}NO_2$: 60.23. Found: 60.18.

The solid mononitro compound was converted to the corresponding trinitro compound (musk sylene) by the following procedure. Four milliliters of fuming nitric acid was added, dropwise with stirring, to a mixture of 1 g. of the nitro compound and 6 ml. of fuming sulfuric acid. The reaction mixture was warmed for fifteen minutes on a steam-bath and poured on cracked ice. The product crystallized from 95% ethanol in white platelets; m.p. 112–113°.

Anal. Calc'd for $C_{12}H_{15}N_3O_6$: C, 48.48; H, 5.05; N, 14.14.
Found: C, 48.61; H, 5.14; N, 14.23.

Nitration of the liquid mononitro compound by a similar procedure yielded a product melting at 109–111°. A mixture of the two nitration products melted at 110–111.5°. Baur (7) reported the trinitro derivative to melt at 110°.

4-t-Butyl-2,6-dimethylacetanilide. A mixture of 91 g. of 4-*t*-butyl-2,6-dimethylnitrobenzene, 400 ml. of water, 5 ml. of concerntrated hydrochloric acid, and 110 g. of iron powder was heated under reflux, with stirring, for five and one-half hours. The solution was made basic by the addition of 10 g. of sodium carbonate, and the precipitate removed by suction filtration. The precipitate was washed with five 100-ml. portions of ether. The ether washings were then used to extract the amine from the aqueous filtrate. Three extractions of this ether solution were made, using 100-ml. portions of dilute hydrochloric acid. The amine hydrochloride was removed by filtration and washed well with ether; yield 94%.

One gram of the amine hydrochloride was treated with 12 ml. of 20% potassium hydroxide solution and 5 ml. of acetic anhydride. The white amide was recrystallized from an ethanol-water mixture; m.p. 162.5–163°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65.
Found: C, 76.96; H, 9.85.

Chichibabin (9) gave the melting point of the acetanilide as 159° and Baur (10) as 81°. Because of this discrepancy the corresponding benzoyl derivative was made. It was found to melt at 229–231° when heated rapidly on the Macquenne block. The melting point reported by Baur (10) for this derivative is 233°.

6-t-Butyl-2,4-dimethylacetanilide. By use of a procedure similar to that just outlined for the symmetrical isomer, 6-*t*-butyl-2,4-dimethylaniline was obtained in 75% yield. The acetanilide, after recrystallization from an ethanol-water mixture, melted at 188–189°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65.
Found: C, 76.66; H, 9.59.

The benzoyl derivative melted at 206–207°. Baur (10) reported the value 206°.

4-t-Butyl-2,6-dimethylbromobenzene. A. *From 4-t-butyl-2,6-dimethylaniline.* The amine was converted into the bromide by use of the Sandmeyer method. From 5 g. of the amine was obtained 4.5 g. of bromide, which separated from ethanol in white platelets melting at 50–51°.

B. *From 5-t-butyl-1,3-dimethylbenzene.* The hydrocarbon was brominated by a procedure similar to that employed by Smith (24) for bromomesitylene. The product, obtained in 93% yield, melted at 48–50° and did not depress the melting point when mixed with the sample described under A. The value given in the literature for the melting point is 45° (8, 9).

Attempts to chloromethylate the bromo compound were unsuccessful.

5-t-Butylhemimellitene. By use of the procedure of Fuson, Denton, and Kneisley (2) 4-*t*-butyl-2,6-dimethylbenzyl chloride was converted to the hydrocarbon in 89.5% yield. The hydrocarbon was made also from 4-*t*-butyl-2,6-dimethylbromobenzene. To a Grignard reagent, prepared from 5 g. of magnesium, 51 g. of the bromo compound, and 750 ml. of dry ether, and cooled to 10°, was added dropwise 104 g. of freshly distilled dimethyl sulfate in 500 ml. of dry ether. After the mixture had stood overnight, the product was isolated according to conventional methods. The butylhemimellitene (12 g.) distilled at 88–90° (4 mm.) and crystallized in the receiver. After one recrystallization from ethanol, it melted at 31–32°. It was shown by the mixed melting point method to be identical with the sample prepared from the chloromethyl compound. The two samples of hydrocarbon yielded the same dinitro derivative (m.p. 134.5–136°).

4-Bromo-5-t-butylhemimellitene. This compound was made by bromination of 5-*t*-butylhemimellitene. A solution of 8.3 g. of bromine in 15 ml. of carbon tetrachloride was added over a period of three hours, with vigorous stirring, to a mixture of 8.8 g. of 5-*t*-butylhemimellitene, 25 ml. of carbon tetrachloride, and 0.4 g. of iron powder. The mixture was cooled in an ice-bath during the addition and for three hours afterward. It was then kept, for eight hours, with continued stirring, at room temperature. The bromide, isolated by the usual procedure, was purified by distillation followed by three recrystallizations from ethanol; m.p. 50–51°. A mixture of this compound with an authentic sample of 4-*t*-butyl-2,6-dimethylbromobenzene (m.p. 49.5–51°) melted at 30–33°.

Anal. Calc'd for $C_{13}H_{19}Br$: C, 61.18; H, 7.50.
Found: C, 60.83; H, 7.56.

4-t-Butyl-2,6-dimethylacetophenone. A. *From 5-t-butyl-1,3-dimethylbenzene.* Anhydrous aluminum chloride (141 g.) was added, with vigorous stirring and over a period of ninety minutes, to a mixture of 75 g. of the hydrocarbon, 195 g. of freshly distilled acetyl chloride, and 350 ml. of carbon disulfide. The mixture was allowed to stand for one hour. The ketone, isolated by conventional procedures, boiled at 107–110° (2.5 mm.) and melted at 45.5–46.5°. It crystallized from methanol in large glistening plates. Baur (5, 10) reported the melting point 48° for the unsymmetrical isomer.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.30; H, 9.87.
Found: C, 82.27; H, 9.97.

The dinitro derivative, prepared by nitration with yellow fuming nitric acid, was recrystallized from methanol; m.p. 135.5–136°.

Anal. Calc'd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16.
Found: C, 57.27; H, 6.34.

B. *From 4-t-butyl-2,6-dimethylbromobenzene.* 4-*t*-Butyl-2,6-dimethylbenzoic acid was prepared in 61% yield by a procedure similar to that of Barnes for mesitoic acid (14). The melting point was 167–168°. The value reported by Baur (5, 10) for the unsymmetrical isomer was 168°.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79.
Found: C, 75.59; H, 8.82.

The dinitro derivative, after repeated recrystallization from methanol, melted at 233–235° when heated rapidly on an aluminum block. Baur (5, 10) gives 236° as the melting point of the unsymmetrical isomer.

Anal. Calc'd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44.
Found: C, 52.22; H, 5.27.

The acid chloride, purified by recrystallization from high-boiling petroleum ether, was found to melt at 59–61°; the value recorded (25) is 62°. The acid chloride was converted to 4-*t*-butyl-2,6-dimethylacetophenone by treatment with dimethylcadmium prepared by the method of Gilman and Nelson (15). One gram of the acid chloride in 10 ml. of dry ether was added gradually to a solution containing approximately a seven-fold excess of dimethylcadmium. The mixture was then heated under reflux, with stirring, for three hours and decomposed by the addition of cracked ice. The ketone, isolated by conventional procedures, was recrystallized from methanol; m.p. 46–47°; yield 34%. A mixture with the sample prepared by method A melted at 45.5–47°.

4-t-Butyl-2,6-dimethylethylbenzene. A. *From 4-t-butyl-2,6-dimethylacetophenone.* The ketone was reduced by a method similar to that employed by Smith and Kiess (16). The yield of redistilled hydrocarbon was 47%; b.p. 125–127° (20 mm.); n_D^{20} 1.5050. Fuson, Denton, and Kneisley (2) gave the following constants; b.p. 125° (20 mm.); n_D^{20} 1.5044.

Two grams of the hydrocarbon was dropped slowly, with stirring, into 60 ml. of yellow fuming nitric acid maintained below 5°. The mixture was allowed to stand at this temperature for one hour. The dinitro compound was removed by filtration and recrystallized eight times from methanol; m.p. 128–129°. The melting point recorded in the literature is 128.5–129° (2).

Anal. Calc'd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 10.00.
Found: C, 59.98; H, 7.36; N, 9.99.

B. *From 4-t-butyl-2,6-dimethylbenzylmagnesium chloride and methyl sulfate.* The method was similar to that used by Gilman and Catlin (17) in the preparation of *n*-propylbenzene. The yield was 34.6%; b.p. 81–84° (4 mm.); n_D^{20} 1.5043. The coupling product, 1,2-di-(2,6-dimethyl-4-*t*-butylphenyl)ethane (m.p. 216–217°), was obtained as a by-product.

The nitration product of the ethyl compound melted at 127–128°. A mixture with the sample described under method A melted at 126–128°.

4-t-Butyl-2,6-dimethylbenzonitrile. A. *From 4-t-butyl-2,6-dimethylbromobenzene.* The bromo compound was converted to the nitrile by a procedure patterned after that of Newman for 1-naphthonitrile (18). The product was purified by distillation; b.p. 104–107° (5 mm.); m.p. 64–66°; yield 67.4%. The analytical sample, after being recrystallized from ethanol, melted at 64.5–65.5°. Baur (10) reported the melting point to be 88°.

Anal. Calc'd for $C_{13}H_{17}N$: C, 82.93; H, 9.63.
Found: C, 82.93; H, 9.42.

The dinitro derivative was prepared by adding one gram of the nitrile, with stirring, to a mixture of 8 ml. of 15% fuming sulfuric acid and 4 ml. of yellow fuming nitric acid (sp. gr. 1.49–1.50) at 3°. The mixture was allowed to stand for one hour at 27° and poured on ice. The yield was 0.8 g.; m.p. 105–108°. The analytical sample was recrystallized five times from 95% ethanol; m.p. 108–109°. The accepted value is 110° (10).

Anal. Calc'd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.16.
Found: C, 56.20; H, 5.66; N, 15.02.

B. *From 4-t-butyl-2,6-dimethylbenzaldehyde.* The aldehyde was obtained from the acid chloride in 77% yield by following closely the procedure of Barnes for 2,4,6-trimethylbenzaldehyde (19). The product was distilled at 100–103° (3 mm.) and solidified immediately in the receiver; m.p. 59–60°.

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.06; H, 9.53.
Found: C, 80.85; H, 9.60.

The *dinitro derivative* of the aldehyde, after repeated recrystallization from 50% ethanol, melted at 110–111°. The value found in the literature is 110° (12).

Anal. Calc'd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75.
Found: C, 55.45; H, 5.75.

The *2,4-dinitrophenylhydrazone* of the dinitro aldehyde separated from ethyl acetate in canary yellow crystals; m.p. 245–246° (slow heating on an aluminum block).

Anal. Calc'd for $C_{19}H_{20}N_6O_8$: C, 49.56; H, 4.38.
Found: C, 49.78; H, 4.54.

The *2,4-dinitrophenylhydrazone* of 4-*t*-butyl-2,6-dimethylbenzaldehyde was recrystallized first from chloroform, then from ethyl acetate; m.p. 217–218°.

Anal. Calc'd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99.
Found: C, 61.81; H, 6.11.

The oxime of 4-*t*-butyl-2,6-dimethylbenzaldehyde was purified by repeated recrystallization from 50% ethanol followed by recrystallization from low-boiling petroleum ether; m.p. 107–108°. The literature records the melting point 97–98° for the unsymmetrical isomer.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33.
Found: C, 76.20; H, 9.29.

A mixture of 1 g. of the oxime and 10 ml. of acetic anhydride was heated under reflux for 20 minutes, cooled, and poured into 100 ml. of cold water. After one hour the solid nitrile was removed by filtration and recrystallized from 95% ethanol; m.p. 65.5–66.5°. A mixture with the sample described under method A melted at 66.0–66.5°.

The dinitro derivative prepared from the nitrile made from the oxime melted at 107–108°. A mixture with the sample described under method A melted at 107.5–108.5°.

C. *From 4-t-butyl-2,6-dimethylaniline.* The amine was converted to the nitrile by a procedure closely similar to that of Clarke and Read for the preparation of *o*-tolunitrile (20). From 16 g. of the amine there was obtained 3.1 g. of nitrile. The nitrile was purified by recrystallization from alcohol and from high-boiling petroleum ether; m.p. 64–65.5°. It did not depress the melting point of the sample made by the Rosenmund-von Braun method.

Similarly, the dinitro derivative (m.p. 106–108°) did not depress the melting point of the sample which was analyzed.

4-t-Butyl-2,6-dimethylglyoxal. 4-*t*-Butyl-2,6-dimethylacetophenone was oxidized by a method similar to that employed by Fuson and Gray (21) for the preparation of mesityl-glyoxal from acetomesitylene. From 10.2 g. of the methyl ketone was obtained 8.9 g. of glyoxal boiling at 122–127° (7 mm.); yield 81.5%. The glyoxal set to a yellow solid, but difficulty was encountered in obtaining a reproducible melting point. The white crystalline hydrate, formed by mixing the glyoxal with boiling water, melted at 81–84°. The *semicarbazone* was purified by recrystallization from 25% ethanol. It formed white plates melting at 187–188°.

Anal. Calc'd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69.
Found: C, 65.19; H, 7.86.

The *2,4-dinitrophenylhydrazone* was recrystallized from a mixture consisting of two parts of benzene and five parts of ethanol. It formed yellow platelets melting at 162–163°.

Anal. Calc'd for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57.
Found: C, 60.07; H, 5..55.

4-t-Butyl-2,6-dimethylbenzophenone. This compound, prepared according to the method of Noelting (22), melted at 106–107.5°; yield 48%.

Anal. Calc'd for $C_{19}H_{22}O$: C, 85.67; H, 8.33.
Found: C, 85.74; H, 8.60.

Noelting believed it had the unsymmetrical structure. However, by analogy with our results with the corresponding acetyl compound we considered the symmetrical structure more probable. In confirmation of this opinion it was found possible to prepare this ketone by the action of phenylmagnesium bromide on 4-*t*-butyl-2,6-dimethylbenzoyl chloride. The procedure was patterned after that employed by Whitmore and Heyd (23) for the synthesis of *t*-butyl neopentyl ketone. A solution of phenylmagnesium bromide, prepared from 3.14 g. of bromobenzene, 0.5 g. of magnesium, and 25 ml. of dry ether, was filtered and added gradually over a period of forty minutes to a solution of 2.25 g. of 4-*t*-butyl-2,6-dimethylbenzoyl chloride in 30 ml. of ether. The product, isolated by conventional procedures, was recrystallized from methanol. It formed glistening platelets melting at 108–109°. A mixed melting point with the sample made by the Friedel-Crafts method was 108–109°. Noelting reported the melting point of the unsymmetrical isomer as 105° (22).

SUMMARY

Musk Tibetene has been proved to be 5-*t*-butyl-4,6-dinitrohemimellitene and not 6-*t*-butyl-3,5-dinitropseudocumene as previously reported. Similarly, musk ketone has been shown to be 4-*t*-butyl-3,5-dinitro-2,6-dimethylacetophenone instead of 6-*t*-butyl-3,5-dinitro-2,4-dimethylacetophenone, the structure assigned long ago by Baur.

URBANA, ILLINOIS.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY
OF THE UNIVERSITY OF MICHIGAN]

REACTIONS OF 1,2,3,4-TETRAHYDROPHENANTHRENE AND DERIVATIVES. III. ALKYL DERIVATIVES AND ANTIMALARIALS

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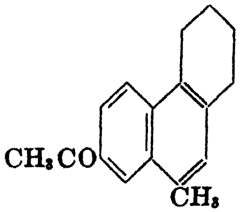
In continuing the study of 1,2,3,4-tetrahydrophenanthrene (1), 9-methyl-, 9-ethyl-, and 7-ethyl-1,2,3,4-tetrahydrophenanthrene were acetylated and succinoylated by means of the Friedel-Crafts reaction. Since tetrahydrophenanthrene acylates (1) and succinoylates (2, 3) in the 7 and 9 positions in the ratio of about 1:2 and 1:3 respectively, it was expected that the 9-alkyl derivatives would be attacked in the 7 position and the 7-alkyl compound in the 9 position. This was found to be the case.

The reaction of acetyl chloride with 9-methyl-1,2,3,4-tetrahydrophenanthrene gave 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene (I). This ketone was reduced by the Clemmensen method to 7-ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrogenated by palladium on charcoal to 7-ethyl-9-methylphenanthrene. The structure of this compound was established by its synthesis from β-ethylnaphthalene. This hydrocarbon was succinoylated and the resulting β-6-ethyl-2-naphthoylpropionic acid was reduced by the Clemmensen method. Cyclization of the acid chloride of the reduced acid with stannic chloride yielded 4-keto-7-ethyl-1,2,3,4-tetrahydrophenanthrene (II), which on Clemmensen reduction gave 7-ethyl-1,2,3,4-tetrahydrophenanthrene. The hydrocarbon was identical with that obtained by Clemmensen reduction of 7-acetyl-1,2,3,4-tetrahydrophenanthrene, which is formed to some extent by acetylation of tetrahydrophenanthrene (1).



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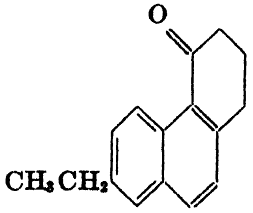

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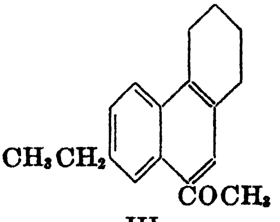

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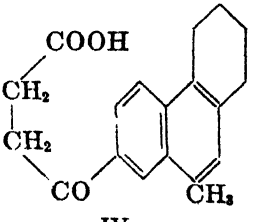

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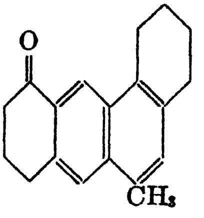

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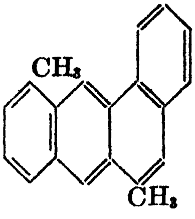

VI

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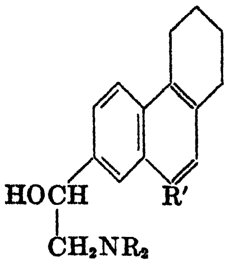

VII

Acetylation of 7-ethyl-1,2,3,4-tetrahydrophenanthrene in carbon disulfide and *sym.*-tetrachloroethane gave 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (III) in good yield. A Willgerodt reaction on III, followed by hydrolysis and a soda-lime fusion on the sodium salt of the resulting acid yielded 7-ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrogenaged to 7-ethyl-9-methylphenanthrene.

Similarly, acetylation of 9-ethyl-1,2,3,4-tetrahydrophenanthrene gave 7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, as was shown by the formation of the same hydrocarbon, 7,9-diethyl-1,2,3,4-tetrahydrophenanthrene, by Clemmensen reduction of the acetyl compound and by Clemmensen reduction of the semicarbazone of the ketone III. Of novel interest is the use of the semicarbazone in the Clemmensen reduction; it yielded the hydrocarbon in good yield. Sulfur dehydrogenation of the diethyltetrahydrophenanthrene gave 7,9-diethylphenanthrene.

Condensation of 9-methyltetrahydrophenanthrene with succinic anhydride and $AlCl_3$ gave only one product, β-9-methyl-1,2,3,4-tetrahydro-7-phenanthroylpropionic acid IV. Its structure was proved in two ways: (a) by synthesis from 7-bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene by the malonic ester synthesis; and (b) by alkali cleavage to 9-methyl-1,2,3,4-tetrahydro-7-phenanthroic acid, which was identical with the acid obtained by the haloform reaction on 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene.

Clemmensen reduction of the keto acid IV gave γ-9-methyl-1,2,3,4-tetrahydro-7-phenanthrylbutyric acid whose acid chloride was cyclized with stannic chloride to 4-methyl-8-keto-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene (V). This result differs markedly from that obtained with the acid not bearing a methyl group in the 9-position, which cyclizes from the 7 to the 8 position with formation of a chrysene derivative (3). It is, however, in agreement with the cyclization of γ-8-methyl-2-naphthylbutyric acid (4) and of γ-5,6,7,8-tetramethyl-2-naphthylbutyric acid (5) to the 3 position rather than to the 1 position, results that have been explained on the basis of the steric effect of the methyl group. Clemmensen reduction of the cyclic ketone gave 4-methyl-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene which was dehydrogenated by palladium on charcoal to 4-methyl-1,2-benzanthracene. Interaction of the

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4-methyl-8-ketooctahydro-1,2-benzanthracene with methylmagnesium iodide gave 8-hydroxy-4,8-dimethyl-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene which on simultaneous dehydration and dehydrogenation with palladium-charcoal at 300–320° was converted into 4,8-dimethyl-1,2-benzanthracene (VI).

While the work on derivatives of 1,2,3,4-tetrahydrophenanthrene was in progress, the possible importance of tetrahydrophenanthrene derivatives as antimalarials became known to us through the work of the National Institute of Health group (6). By arrangement with Dr. L. F. Small a number of 7-α-hydroxy-β-dialkylaminoethyl-9-alkyl-1,2,3,4-tetrahydrophenanthrenes VII were synthesized to supplement their work. These compounds were obtained by condensing dialkyl amines with 7-bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene and then reducing the amino ketones with aluminum isopropoxide. The products, most of which are oils, are listed in Table I. The activities of the compounds are reported in a monograph of the Survey of Antimalarial Drugs (12).

EXPERIMENTAL

α-4-Methyl-1-naphthylbutyric acid. A mixture of 18.5 g. of β-4-methyl-1-naphthoylpropionic acid (6), 50 g. of amalgamated zinc, 75 cc. of concentrated hydrochloric acid, 75 cc. of acetic acid, and 50 cc. of toluene was refluxed for twenty-four hours, an additional 75 cc. of concentrated hydrochloric acid being added in portions over this time. The toluene layer was separated and evaporated. The residue crystallized from benzene in colorless needles; m.p. 158.5–159.5°; weight, 16.1 g. (93%). The melting point was unchanged after two more recrystallizations from benzene.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 79.0; H, 7.0.
Found: C, 78.6; H, 7.0.

1-Keto-9-methyl-1,2,3,4-tetrahydrophenanthrene. To a solution of 11.2 g. of the aforementioned acid in 100 cc. of dry ether and 10 drops of pyridine was added 20 cc. of thionyl chloride. After the mixture had stood at room temperature for one-half hour, the ether and thionyl chloride were evaporated under reduced pressure. To a solution of the acid chloride in 100 cc. of dry benzene cooled in ice-water, 15 cc. of stannic chloride was added with swirling. After five minutes the complex was decomposed with ice and hydrochloric acid. The benzene layer was washed with dilute ammonium hydroxide, and the benzene was evaporated. The residue crystallized from petroleum ether in colorless needles; weight, 9.64 g. (94%); m.p. 75.5–76°. After two more recrystallizations from petroleum ether the ketone melted at 76–77° [reported (7), 74–75°].

9-Methyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 5.82 g. of 1-keto-9-methyl-1,2,3,4-tetrahydrophenanthrene, 30 g. of amalgamated zinc, 45 cc. of concentrated hydrochloric acid, 45 cc. of acetic acid, and 25 cc. of toluene was refluxed for twenty-four hours. An additional 45 cc. of concentrated hydrochloric acid was added in portions over this period. The toluene layer was separated, the toluene was evaporated, and the residue was distilled at 0.4 mm. The colorless distillate was dissolved in hot alcohol and 5.8 g. of picric acid was added. On cooling, the solution deposited 10 g. of picrate; yield, 85%; m.p. 114–115°. In further experiments the liquid hydrocarbon was used without purification through the picrate.

The pure *picrate* crystallized from alcohol in reddish-orange needles; m.p. 114–115.5°.

Anal. Calc'd for $C_{21}H_{19}N_3O_7$: N, 9.9. Found: N, 9.7.

A mixture of 0.42 g. of 9-methyl-1,2,3,4-tetrahydrophenanthrene and 0.04 g. of palladium-charcoal catalyst (8) was heated at 300–320° for one hour. The mixture was taken up in hot acetone and filtered. The hydrocarbon obtained by evaporation crystallized from alcohol in colorless needles; yield, 0.34 g. (83%); m.p. 91.5–92.5°. A mixture of the hydro-

TABLE I

SUBSTITUTED AMINO ALCOHOLS REPRESENTED BY FORMULA VII

SN	R′	R	DERIVATIVE ANALYZED	CRYST. FORM[a]	M.P. °C.	ANAL.					
						Calc'd			Found		
						C	H	N	C	H	N
7953-S₁	CH_3	n-C_4H_9	Picrate	Yellow platelets	170.5–171.5	62.40	6.76	9.39	62.30	6.63	9.20
7956-S₁	CH_3	n-C_5H_{11}	Picrate	Yellow prisms	140–141	63.44	7.10	8.97	63.18	7.00	9.20
7957	CH_3	iso-C_5H_{11}	Picrate	Yellow prisms	139–140	63.44	7.10	8.97	63.16	6.98	9.20
7959-S₁	CH_3	n-C_6H_{13}	Picrate	Yellow prisms	136–138	64.40	7.44	8.58	64.25	7.36	8.60
7958-S₁	CH_3	iso-C_6H_{13}	Picrate	Orange prisms	118.5–120	64.40 60.12	7.44 6.57	8.58[b] 9.85[c]	59.88	6.61	10.06
7954-S₁	CH_3	cyclohexyl	Picrate	Yellow needles	192–193	64.80	6.84	8.80	64.13	6.93	8.80
7955	CH_3	NR_2 = Tetrahydroquinoline	Free base	Colorless needles	131–132	84.05	7.87	3.77	83.57	7.99	3.82

[a] All compounds were recrystallized from ethanol.

[b] Calc'd for monopicrate.

[c] Calc'd for sesquipicrate.

carbon and authentic 9-methylphenanthrene (m.p. 90–91°) prepared from 9-phenanthrylmagnesium bromide and methyl iodide (9) melted at 90–91°.

7-Acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. Five grams of 9-methyltetrahydrophenanthrene was added to an ice-cold solution of 6.6 g. of aluminum chloride and 2 cc. of acetyl chloride in 20 cc. of nitrobenzene and the mixture was kept in a refrigerator for twenty hours. The nitrobenzene was removed by steam distillation from the hydrolyzed mixture, the residue was dissolved in benzene, the filtered benzene solution was evaporated, and the acetyl compound was crystallized from alcohol; weight, 4.14 g. (68%); m.p. 96–97.5°. After two recrystallizations from alcohol, the colorless prisms melted at 98–100°.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6. Found: C, 85.7; H, 7.6.

7-Ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 1 g. of 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 5 cc. of toluene was refluxed for twenty-four hours. An additional 30 cc. of a 1:1 mixture of acetic acid and concentrated hydrochloric acid was added in portions over this time. The toluene layer was separated, the toluene was evaporated, and the hydrocarbon was evaporatively distilled at 220° and 0.4 mm. A solution of the colorless oily distillate and 0.9 g. of picric acid in hot absolute alcohol deposited 1.55 g. of the (82%) picrate; m.p. 119–120°. For the subsequent dehydrogenation the hydrocarbon was obtained by decomposition of the picrate with dilute ammonium hydroxide.

The *picrate* crystallized from acetone-alcohol in red needles; m.p. 119.5–120°.

Anal. Calc'd for $C_{23}H_{23}N_3O_7$: N, 9.3. Found: N, 9.1.

7-Ethyl-9-methylphenanthrene. A mixture of 0.69 g. of 7-ethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene and 0.08 g. of palladium-charcoal catalyst (8) was heated for one hour at 300–320°. The mixture was taken up in hot acetone and filtered. The acetone was evaporated, and the colorless oily residue was dissolved in hot alcohol and treated with 0.75 g. of picric acid. The solution deposited 1.29 g. of picrate; yield, 93%; m.p. 106–108°.

The *picrate* crystallized from alcohol-acetone in bright orange prisms; m.p. 107–108°.

Anal. Calc'd for $C_{23}H_{19}N_3O_7$: N, 9.4.
Found: N, 9.2.

β-6-Ethyl-2-naphthoylpropionic acid. β-Ethylnaphthalene was prepared by refluxing a mixture of 100 g. of β-acetylnaphthalene, 400 g. of amalgamated zinc, 600 cc. of concentrated hydrochloric acid, 600 cc. of glacial acetic acid, and 400 cc. of toluene for twenty-four hours with the addition of 600 cc. of hydrochloric acid over this time. After separation of the toluene layer, washing with water, and removal of the toluene, the β-ethylnaphthalene was distilled under reduced pressure; b.p. 100–102° at 2 mm.; yield, 78 g. (85%).

To an ice-cooled solution of 146 g. of aluminum chloride and 110 g. of succinic anhydride in 500 cc. of *sym.*-tetrachloroethane was added 78 g. of β-ethylnaphthalene dropwise with good stirring. After the addition of the hydrocarbon the mixture was stirred for an hour and a half in the ice-bath, kept in a refrigerator for twenty-four hours, and then hydrolyzed with ice and hydrochloric acid. After a recrystallization from benzene, the acid weighed 85 g. and melted at 152–155°. After two recrystallizations from acetone a sample formed colorless prisms; m.p. 171–172°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3.
Found: C, 74.7; H, 6.3.

α-6-Ethyl-2-naphthylbutyric acid. A mixture of 73 g. of the aforementioned acid, 400 g. of amalgamated zinc, 600 cc. of concentrated hydrochloric acid, 600 cc. of glacial acetic acid, and 400 cc. of toluene was refluxed for twenty-four hours with the addition of 600 cc. of hydrochloric acid over this time. The warm toluene layer was separated, the aqueous layer was shaken with benzene and the combined organic solutions were concentrated; yield, 54 g. (78%); m.p. 114–118°. After two recrystallizations from benzene the nacreous leaflets melted at 120.5–121.5°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5.
Found: C, 79.2; H, 7.3.

4-Keto-7-ethyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 45 g. of the aforementioned butyric acid, 42.5 g. of phosphorus pentachloride, and 175 cc. of dry benzene was allowed to stand for one hour with occasional swirling, was warmed for five minutes on a steam cone, and was then cooled in ice until the benzene started to crystallize. To this solution was added rapidly 48 cc. of stannic chloride in 50 cc. of benzene, the mixture was swirled intermittently for seven minutes and was then hydrolyzed in crushed ice and concentrated hydrochloric acid. After the mixture had been washed with concentrated hydrochloric, dilute hydrochloric, water, and dilute ammonium hydroxide, the benzene was evaporated; yield of ketone, 38 g. (91%); m.p. 46–48°. A sample of the ketone formed colorless prisms after two recrystallizations from benzene-petroleum ether; m.p. 48.5–50°.

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.7; H, 7.2.
Found: C, 85.6; H, 7.2.

7-Ethyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 36 g. of 4-keto-7-ethyl-1,2,3,4-tetrahydrophenanthrene, 200 g. of amalgamated zinc, 300 cc. of concentrated hydrochloric acid, 300 cc. of glacial acetic acid, and 200 cc. of toluene was refluxed for twenty-four hours with the addition of 300 cc. of concentrated hydrochloric acid over this time. The product isolated from the toluene layer was distilled under reduced pressure; b.p. 140° at 0.1 mm.; yield, 33 g. (98%). The picrate was obtained as yellow needles from ethanol; m.p. 90–91°. A mixed melting point with the picrate of 7-ethyl-1,2,3,4-tetrahydrophenanthrene (1) obtained by reduction of the 7-acetyl derivative gave no depression.

7-Ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. To a mixture of 32 g. of aluminum chloride and 19 g. of acetyl chloride in 340 cc. of carbon disulfide which had been stirred at room temperature for fifteen minutes was added 230 cc. of *sym.*-tetrachloroethane and then a solution of 23.5 g. of 7-ethyl-1,2,3,4-tetrahydrophenanthrene in 40 cc. of carbon disulfide. After being stirred for half an hour at room temperature the mixture was placed in a refrigerator overnight. The product which was isolated in the usual manner was distilled under reduced pressure; b.p. 180° at 0.05 mm.; yield, 26 g. (92%). The ketone crystallized from methanol in colorless plates; yield, 21 g. (74%); m.p. 43–45°. After two more recrystallizations a sample melted at 45.5–47°.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.6; H, 8.0.
Found: C, 85.8; H, 8.0.

The *semicarbazone* after several recrystallizations from ethyl acetate formed colorless needles; m.p. 223.5–224.5° dec.

Anal. Calc'd for $C_{19}H_{23}N_3O$: N, 13.6. Found: N, 13.3.

7-Ethyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid amide. 7-Ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (2 g.) was heated in a sealed tube at 170–175° for twenty-four hours with 10 g. of concentrated ammonium hydroxide saturated with hydrogen sulfide, 2 g. of sulfur, and 8 cc. of dioxane. The amide (0.8 g.; m.p. 188–192°) obtained by recrystallization of the crude reaction product from chlorobenzene was recrystallized twice from ethyl acetate; the colorless needles melted at 192.5–193.5°.

Anal. Calc'd for $C_{18}H_{21}NO$: C, 80.76; H, 7.92; N, 5.2.
Found: C, 80.79; H, 7.63; N, 5.1.

7-Ethyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid. A mixture of 1.3 g. of the aforementioned acid amide, 25 cc. of glacial acetic acid, 11 cc. of concentrated hydrochloric acid, and 25 cc. of water was refluxed for twenty-four hours. Dilution of the product with 50 cc. of concentrated hydrochloric acid precipitated 1.1 g. (85%) of the desired acid; m.p. 171–173°. After two recrystallizations from acetone a sample formed colorless needles; m.p. 173–174.5°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5.
Found: C, 80.6; H, 7.5.

A mixture of the dry sodium salt from 0.16 g. of the acid and 0.5 g. of soda-lime was heated in a sublimation tube under 0.05 to 0.1 mm. pressure at 300–320° for four to five hours. A colorless oil (0.075 g.) was obtained. Since previous experiments had shown this to be a mixture containing some dehydrogenated product it was dehydrogenated directly by heating with palladium-charcoal catalyst (8) at 300–320° for one hour. After filtration of the catalyst and evaporation of the benzene, an alcoholic solution of the resulting oil with picric acid deposited 0.13 g. of bright orange prisms; m.p. 103–106°. After recrystallization from absolute alcohol the picrate melted at 108–109° alone and when mixed with a sample of the picrate of 7-ethyl-9-methylphenanthrene prepared as described previously.

7-Bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. To an ice-cold solution of 1 g. of 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene in 40 cc. of dry ether was added a cold solution of 0.72 g. of bromine in 20 cc. of ether, and the mixture was allowed to stand in the cold for one-half hour. The precipitated bromide was filtered off and the filtrate was evaporated to obtain a second crop; total weight, 1.1 g. (83%); m.p. 120–121.5°. After two recrystallizations from acetone-methanol the colorless needles melted at 123.5–124°.

Anal. Calc'd for $C_{17}H_{17}BrO$: Br, 25.2. Found: Br, 26.0.

β-9 Methyl-1,2,3,4-tetrahydro-7-phenanthroylpropionic acid. (a) A mixture of 0.08 g. of powdered sodium, 0.75 cc. of malonic ester, and 10 cc. of benzene was refluxed until all of the sodium had reacted and then 0.59 g. of 7-bromoacetyl-9-methyltetrahydrophenanthrene was added. The mixture was allowed to stand at room temperature overnight and was then heated on a steam-bath for six hours. Dilute hydrochloric acid was added, the benzene layer was washed with water, and the benzene was evaporated. The residue was hydrolyzed with hot 40% potassium hydroxide solution, water was added to dissolve the potassium salt formed, and the solution was filtered and acidified. The precipitated acid was heated at 180° for one-half hour and the product was recrystallized from acetic acid; weight, 0.46 g. (84%); m.p. 212–215°. After two further recrystallizations from acetic acid-toluene it melted at 215.5–217°.

(b) To an ice-cold solution of 11.8 g. of aluminum chloride and 4.8 g. of succinic anhydride in 50 cc. of nitrobenzene was added 8.5 g. of 9-methyltetrahydrophenanthrene. The mixture was allowed to stand in a refrigerator for twelve hours, ice and hydrochloric acid were added to hydrolyze the complex, and the nitrobenzene layer was steam distilled. The residue was taken up in hot dilute sodium hydroxide solution and the filtered solution was acidified. The precipitated acid (12 g.; m.p. 183–193°) was recrystallized from toluene-acetic acid; weight, 7.9 g.; m.p. 211–214°. After two more recrystallizations the acid formed colorless needles; m.p. 215.5–217° alone and when mixed with the acid prepared in part (a).

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8.
Found: C, 76.9; H, 6.7.

γ-9-Methyl-1,2,3,4-tetrahydro-7-phenanthrylbutyric acid. A mixture of 3 g. of the aforementioned keto acid, 15 g. of amalgamated zinc, 23 cc. of concentrated hydrochloric acid, 23 cc. of acetic acid, and 10 cc. of toluene was refluxed for twenty-four hours, an additional 20 cc. of concentrated hydrochloric acid being added in portions over this time. The acid isolated from the toluene layer crystallized from benzene in clusters of colorless needles; weight, 2.55 g. (89%,; m.p. 141–143°. After two recrystallizations from benzene the acid melted at 142.5–144°.

Anal. Calc'd for $C_{19}H_{22}O_2$: C, 80.9; H, 7.8.
Found: C, 80.7; H, 7.8.

4-Methyl-8-keto-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene. To a mixture of 2.55 g. of the aforementioned butyric acid, 25 cc. of dry ether, and 2 drops of pyridine, was added 5 cc. of thionyl chloride. The mixture was allowed to stand at toom temperature for one-half hour after the acid had dissolved, the ether and thionyl chloride were removed under reduced pressure, and the acid chloride was dissolved in 25 cc. of dry benzene. To the cooled solution was added 4 cc. of stannic chloride, and the mixture was allowed to stand at room temperature for fifteen minutes. Ice and dilute hydrochloric acid were added to decompose the complex, the benzene layer was washed with dilute ammonium hydroxide and with water, and the benzene was evaporated. The residue crystallized from alcohol in colorless prisms; yield, 2.16 g. (91%); m.p. 109–110.5°. After two recrystallizations from alcohol the ketone melted at 111–112°.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.4; H, 7.6.
Found: C, 86.2; H, 7.6.

4-Methyl-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene. A mixture of 1 g. of 4-methyl-8-ketooctahydro-1,2-benzanthracene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 5 cc. of toluene was refluxed for twenty-four hours, an additional 20 cc. of a 1:1 mixture of acetic and concentrated hydrochloric acids being added in portions over this period. The product isolated from the toluene layer was evaporatively distilled at 220° and 0.4 mm. The distillate crystallized from acetone-alcohol in colorless prisms; weight, 0.74 g. (78%); m.p. 70–72°. After two recrystallizations from acetone-alcohol the hydrocarbon melted at 71–72.5°.

Anal. Calc'd for $C_{19}H_{22}$: C, 91.2; H, 8.8.
Found: C, 90.8; H, 8.6.

The *picrate* crystallized from alcohol in deep red needles; m.p. 183–184°.

Anal. Calc'd for $C_{25}H_{25}N_3O_7$: N, 8.8. Found: N, 8.7.

4-Methyl-1,2-benzanthracene. A mixture of 0.31 g. of 4-methyloctahydro-1,2-benzanthracene and 0.05 g. of palladium-charcoal catalyst (8) was heated at 300–320° for one hour. The mixture was taken up in benzene and the filtered benzene solution was evaporated. The hydrocarbon crystallized from acetone-alcohol in colorless needles; weight, 0.26 g. (87%); m.p. 122–124°. After several crystallizations from acetone-alcohol the hydrocarbon melted at 124.5–125°. The picrate melted at 149–150° and the quinone at 164–165°. These values are in agreement with those reported by Cook (10) and by Fieser and Jones (11).

4,8-Dimethyl-8-hydroxy-1′,2′,3′,4′,5,6,7,8-octahydro-1,2-benzanthracene. To an ice-cold solution of a Grignard reagent made from 1.2 cc. of methyl iodide in 15 cc. of dry ether was added a cooled solution of 1.57 g. of 4-methyl-8-ketooctahydro-1,2-benzanthracene in 15 cc. of dry benzene. After standing cold for ten hours, the solution was shaken with ice and ammonium chloride solution, the organic layer was separated, and the ether and benzene were evaporated in the cold. The residue crystallized from benzene-petroleum ether in colorless, diamond-shaped prisms; yield, 1.5 g. (87%); m.p. 131–133°. After two recrystallizations from benzene-petroleum ether the carbinol melted at 133–134°. It gives a brown color with sulfuric acid.

Anal. Calc'd for $C_{20}H_{24}O$: C, 85.7; H, 8.6.
Found: C, 85.6; H, 8.5.

4,8-Dimethyl-1,2-benzanthracene. A mixture of 0.5 g. of the aforementioned carbinol and 0.08 g. of palladium-charcoal catalyst was heated in a nitrogen atmosphere at 300–320° for one hour. The mixture was taken up in benzene, and the filtered benzene solution was evaporated. The hydrocarbon crystallized from benzene-alcohol in colorless needles; weight, 0.41 g. (90%); m.p. 142.5–144°. After two recrystallizations from benzene-alcohol the hydrocarbon melted at 144°.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.8; H, 6.3.
Found: C, 93.8; H, 6.4.

The *picrate* crystallized from alcohol-acetone in deep red needles; m.p. 175–176°.

Anal. Calc'd for $C_{26}H_{19}N_3O_7$: N, 8.7. Found: N, 8.6.

9-Methyl-1,2,3,4-tetrahydro-7-phenanthroic acid. (a) A suspension of 2.18 g. of 7-acetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene in 110 cc. of 3% sodium hypochlorite solution and 2 cc. of 45% potassium hydroxide solution was refluxed for one hour. The solution was filtered, sodium bisulfite was added to destroy the remaining hypochlorite, and the solution was acidified; weight of product, 1.95 g. (89%); m.p. 264–266.5°. After two recrystallizations from acetic acid-toluene, colorless prisms were obtained; m.p. 269–270°.

(b) A mixture of 0.5 g. of β-9-methyl-1,2,3,4-tetrahydro-7-phenanthroylpropionic acid and 0.8 g. of powdered potassium hydroxide was heated over a free flame for about three minutes. Water was added and the aqueous solution was extracted with benzene and acidified; weight, 0.12 g. (30%); m.p. 230—240°. The acid was recrystallized from toluene-acetic acid, sublimed at 250° and 0.4 mm. and recrystallized again; m.p. 268–269° alone and when mixed with the acid prepared in part (a).

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 79.98; H, 6.71.
Found: C, 79.60; H, 6.80.

7-Acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene. To a well stirred, cooled solution of 97 g. of aluminum chloride and 59 g. of acetyl chloride in 1100 cc. of carbon disulfide which had been stirred for fifteen minutes at room temperature was added 700 cc. of *sym.*-tetrachloroethane followed by 68 g. of 9-ethyl-1,2,3,4-tetrahydrophenanthrene dissolved in 140 cc. of carbon disulfide. The mixture was stirred for thirty minutes in the cold and forty-five minutes at room temperature and then placed in a refrigerator overnight. The mixture was hydrolyzed, the solvent was removed, and the product was distilled under reduced pressure; b.p. 202–204° at 0.3–0.4 mm. Crystallization of the distillate from alcohol gave 63 g. (77%) of ketone; m.p. 82–83.5°. Two more recrystallizations of a sample from ethanol gave colorless needles with the melting point 82–83°.

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.6; H, 8.0.
Found: C, 85.3; H, 7.9.

7,9-Diethyl-1,2,3,4-tetrahydrophenanthrene. (a) A mixture of 0.76 g. of 7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 6 cc. of toluene was refluxed for twenty-four hours with the addition of 30 cc. of a 1:1 mixture of hydrochloric acid and acetic acid during this time. Separation of the toluene, followed by washing with water, drying, evaporation, and sublimation of the residue gave 0.68 g. (95%) of an oil. A solution of the hydrocarbon in alcohol with 0.8 g. of picric acid gave 0.9 g. of a picrate. Two recrystallizations of a sample from ethanol gave long red needles; m.p. 120.5–122°.

(b) Clemmensen reduction, using the same proportions as above, on 0.37 g. of the semicarbazone of the isomeric 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene gave 0.25 g. of hydrocarbon sublimate which deposited 0.4 g. of a *picrate* from alcohol. Recrystallization from alcohol gave long red needles; m.p. 120.5–122° alone and when mixed with the picrate of part (a).

Anal. Calc'd for $C_{24}H_{25}N_3O_7$: C, 61.66; H, 5.39; N, 8.98.
Found: C, 61.46; H, 5.18; N, 8.77.

7,9-Diethylphenanthrene. A mixture of 0.3 g. of 7,9-diethyl-1,2,3,4-tetrahydrophenanthrene regenerated from the crude picrate and 80 mg. of sulfur was heated at 200–220° for one hour in a carbon dioxide atmosphere. Sublimation of the product gave 0.24 g. of hydrocarbon which deposited 0.26 g. of *picrate* when mixed with 0.25 g. of picric acid in alcohol; m.p. 100–103°. Two recrystallizations from ethanol gave golden needles with the m.p. 104–105°. The same results were obtained from the hydrocarbon prepared in (b) above.

Anal. Calc'd for $C_{24}H_{21}N_3O_7$: C, 62.19; H, 4.57; N, 9.06.
Found: C, 62.41; H, 4.48; N, 8.89.

7-Bromoacetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene. To a suspension of 61 g. of 7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene in 800 cc. of ether cooled to 5–10°, 40 g. of bromine was added dropwise at such a rate that each drop was decolorized before the next drop was added. The orange-red addition complex soon broke up to give a flocculent white precipitate of the bromo ketone. After the mixture had come to room temperature, the first crop of bromo ketone was collected and washed with ether. The ether solutions were combined and washed with dilute sodium bicarbonate and water, and the ether was removed by distillation. The total yield of the brominated product was 68 g. (85%); m.p. 90–92°. After two recrystallizations from ethanol a sample formed colorless prisms; m.p. 92–93.5°.

Anal. Calc'd for $C_{18}H_{19}BrO$: C, 65.26; H, 5.78; Br, 24.1.
Found: C, 65.31; H, 5.92; Br, 24.3.

7-α-Hydroxy-β-dibutylaminoethyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. To a solution of 5.7 g. of di-*n*-butylamine[3] in 15 cc. of dry benzene at room temperature was added in portions, with stirring, 7.0 g. of 7-bromoacetyl-9-methyl-1,2,3,4-tetrahydrophenanthrene. The mixture was warmed on a steam cone for ten minutes, cooled in refrigerator, and the precipitated dibutylamine hydrobromide filtered and washed well with cold ether. The ether-benzene solution was washed several times with water, once with 5% sodium hydroxide, and with water. Acidification of the alkaline solution gave 0.2–0.7 g. of an acid, identical with 9-methyl-1,2,3,4-tetrahydro-7-phenanthroic acid, as shown by a mixed melting point. The amount of acid seemed to depend on how long the mixture had stood before being treated with the alkali. The ether-benzene solution was dried over magnesium sulfate and was transfered to the reduction flask. The solvents were removed in a current of air, since heating caused formation of more acid. The residue was refluxed for three hours with 75 cc. of 1.5 *M* aluminum isopropoxide, the mixture was poured into 100 cc. of 10% sodium hydroxide, benzene was added, and the alkaline solution was extracted twice with portions of benzene. The benzene was washed twice with water and dried, and the solvent was removed. To the residue (4.7 g.) was added the theoretical amount (2.9 g.) of picric acid in 25 cc. of absolute alcohol. The mixture was heated on a steam-bath until a clear solution was obtained and then cooled; the alcohol was removed and the residue was triturated with ether. The crude picrate was recrystallized from absolute ethanol; yield, 6.4 g. (49%); m.p. 170–171.5°. Two recrystallizations from absolute ethanol gave yellow platelets melting at 170.5–171.5°.

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[3] We are grateful to Dr. R. C. Elderfield for generous supplies of the amines and for information on the preparation of the amino alcohols.

This same procedure with minor modifications was used for the other amine condensations and reductions, except for the tetrahydroquinolino derivative which separated as the hydrobromide and was reduced as such.

SUMMARY

The Friedel-Crafts reaction with 9-methyl- and 9-ethyl-tetrahydrophenanthrenes gives predominantly the 7 derivative. Several 7-β-hydroxy-β-dialkylaminoethyl-9-methyl-1,2,3,4-tetrahydrophenanthrenes have been made and tested for antimalarial activity.

4-Methyl- and 4,8-dimethyl-1,2-benzanthracene have been synthesized.

ANN ARBOR, MICH.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY,
SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA]

CHEMICAL REACTIONS OF NITROGEN MUSTARD GASES.[1] I. REACTIONS OF METHYL-BIS(β-CHLOROETHYL)AMINE WITH HEXAMETHYLENETETRAMINE

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Previous work in this laboratory (1) has demonstrated that aqueous solutions of methyl-bis(β-chloroethyl)amine (M.B.A.) are rendered non-toxic by exposure to hexamethylenetetramine (H.M.T.). Furthermore, the administration of H.M.T. to animals will to a significant degree protect them against subsequent exposure to M.B.A., regardless of whether the toxic agent is administered subcutaneously as the hydrochloride, or whether it is applied to the skin as the free base.

This report is concerned with a detailed study of the reaction between M.B.A. and H.M.T. undertaken with the hope that information might be obtained concerning the nature of this detoxication.

Reaction of M.B.A. and H.M.T. in water. When aqueous solutions of M.B.A. and H.M.T. are mixed, the following events occur:

1. The resulting solution after standing less than 30 minutes is non-lethal when injected subcutaneously in four lethal doses. Although some toxic effects can be observed when large amounts of the solution are administered, these effects do not appear after the mixture has been allowed to stand for 1–2 hours.

2. After standing 30 minutes with H.M.T. the solution contains approximately equal amounts of ionic and covalent chloride. Chloride ions are liberated at about the same rate (at *p*H 7.5) irrespective of whether H.M.T. is present or not.

3. The color developed by M.B.A. with various reagents (which are specific for organic molecules containing covalent chlorine) fades at the same rate in the presence or absence of H.M.T. (1).

4. After standing 30 minutes, aqueous solutions containing M.B.A. and 2–3 moles of H.M.T. react to only a very slight extent when treated with thiosulfate for 10 minutes. This procedure which was developed by Golumbic, Fruton, and Bergmann (2) serves as a measure of ethylenimonium ions (II, Fig. 1) remaining in the solution. Fruton, Stein, Stahmann, and Golumbic (3) have utilized thiosulfate titration as a measure of the reactivity of test substances toward the nitrogen mustards. These authors were also able to show that H.M.T. reacts extremely rapidly with M.B.A. (3). Our results confirm the conclusions of these investigators, namely that there is very little of the ethylenimine form of M.B.A. left after exposure to H.M.T. for 30 minutes.

These results have led to the following interpretation. Among the products of

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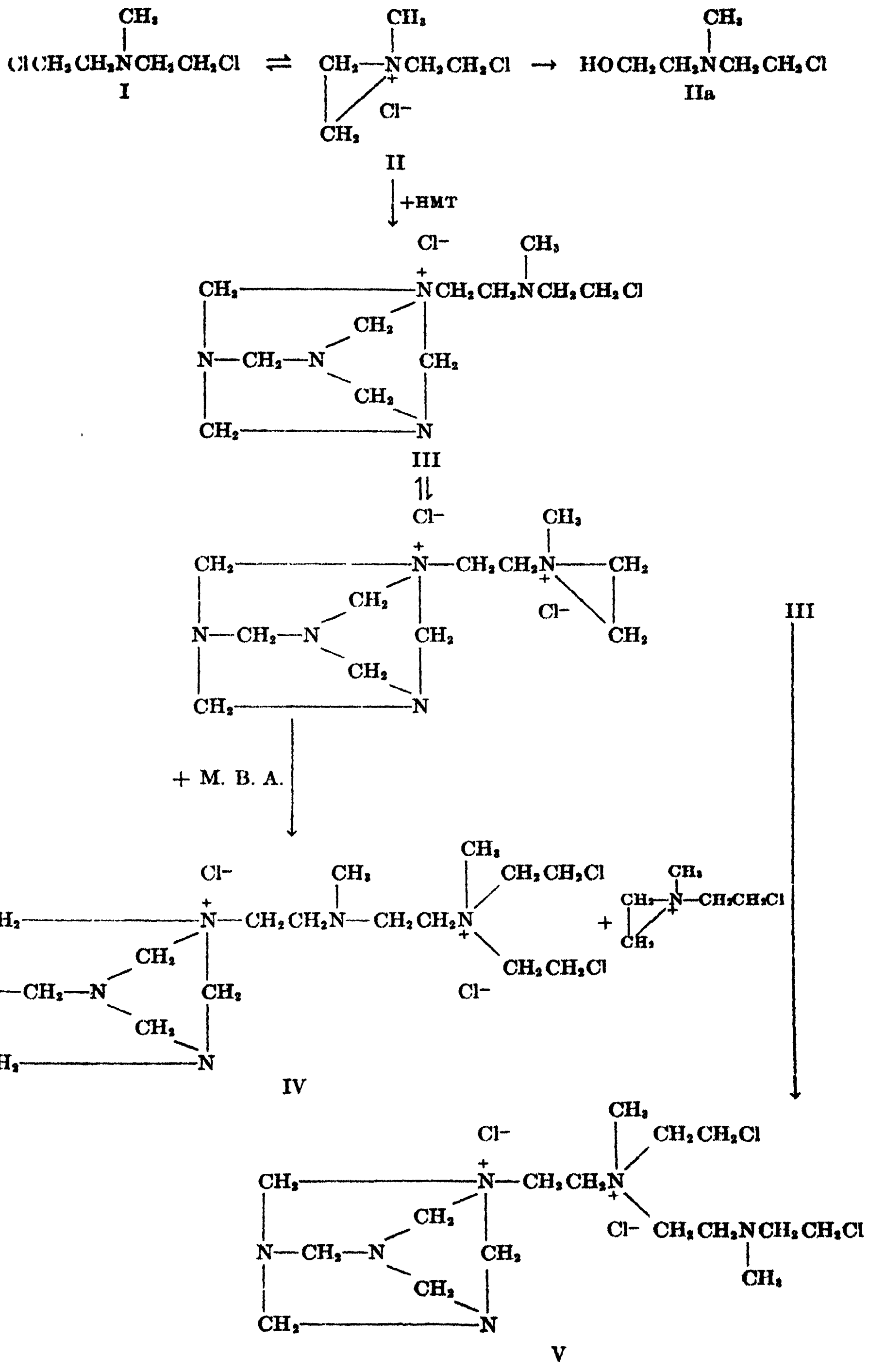
[1] This work was done in whole under Contract No. OEM-cmr-108 between the University of Pennsylvania and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein.

FIG. 1



the reaction it should be possible to find substances containing carbon-bound chlorine. The covalent chlorine atom is not concerned with the rapid condensation occurring during the first 30 minutes. The neutralizing properties of H.M.T. cannot be ascribed to its effect upon the rate of hydrolysis of M.B.A. since chloride ion is liberated at equal rates in the absence or presence of H.M.T. The rate of reaction as well as the mild conditions employed suggest the participation of a reactive chlorine in this reaction. The absence of the ethylenimonium form as indicated by the thiosulfate titration suggests that it is primarily the corresponding ethylenimonium form which reacts rapidly with H.M.T. Since formaldehyde, ammonia, and methylamine each react sluggishly or not at all with M.B.A., it appears that it is intact H.M.T. which participates in the reaction. All of the evidence is in accord with the belief that the ethylenimine form of M.B.A. reacts rapidly with H.M.T. to form quaternary salts. The formation of other quaternary salts of M.B.A. has been described by Golumbic, Fruton, and Bergmann (4).

When equimolar amounts of M.B.A. and H.M.T. were mixed and allowed to stand in 50% aqueous ethanol for 30 minutes, a variety of products was isolated. Among them were H.M.T., H.M.T. hydrochloride, a small amount of β-chloroethylmethylethanolamine (IIa) and considerable quantities of the hexamethylene tetraminium derivative of M.B.A. (III). Evidence was also obtained for the existence of small quantities of a quaternary salt of H.M.T. with a linear dimer of M.B.A.

The quaternary salts are difficult to prepare in pure form. They are soluble in cold water, methanol, warm ethanol, less soluble in chloroform, and slightly soluble in acetone and ether. On warming, they decompose readily, causing brown amorphous products to be formed. Although the nature of these decomposition products has not been investigated, it is suggested that there is a ready loss of HCl, producing vinyl amines accompanied by cleavage of the hexamethylene tetramine portion as a result of the liberated acid.

The analytical data indicate that these substances are monomeric and linear dimeric derivatives of M.B.A. with H.M.T. Peters and Ogston (5) have isolated a picrate to which they tentatively assign the structure of a linear dimer of M.B.A. Golumbic, Fruton, and Bergmann (4) have isolated from the hydrolysis products of 1-methyl-1-(β-chloroethyl)ethylenimonium picrylsufonate a linear dimer (X) which was characterized as a picrylsulfonate and as a Reineckate.

Since the rate of reaction of M.B.A. with H.M.T. is much greater than is the rate of polymerization of M.B.A., it is suggested that the primary reaction is a condensation of H.M.T. with the ethylenimonium form of M.B.A., resulting in the formation of large amounts of product (III). This is supported by the isolation of considerable amounts of this substance.

Although the analytical evidence for product VI is not satisfactory, fairly good evidence has been obtained for VII. While there is very little question concerning the mode of formation of III, there are several routes by which the dimeric salts may be formed. The monomeric quaternary salt III may react with a second molecule of M.B.A. to form either IV or V (Figure 1) which can

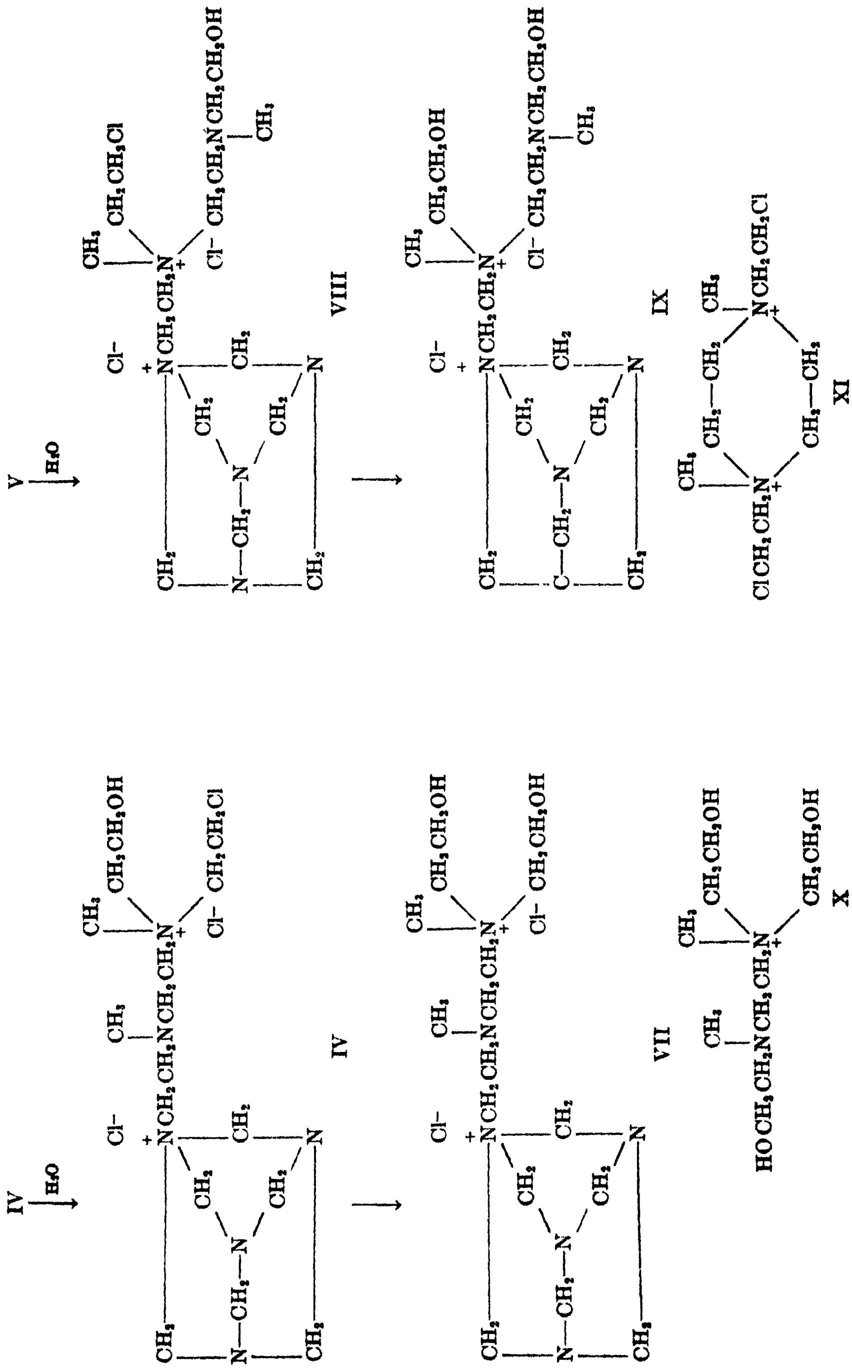


FIG. 2

hydrolyze further to VI, VII, VIII and IX. Product III could, however, condense with β-chloroethylmethylethanolamine (IIa) yielding VI or VIII directly. It is, of course, conceivable that such products may result from a preliminary dimerization of M.B.A. followed by condensation of the resulting linear dimer with H.M.T. Although this mechanism is unlikely, there is as yet not enough information available to make a decision concerning either the mode of formation or the structure of the resulting compounds.

A small amount of impure product VII has been recovered from an aqueous solution of H.M.T. and M.B.A. which had been allowed to stand at room temperature for 24 hours.

The reaction has also been carried out in large volumes of water, thus avoiding the use of 50% aqueous alcohol as a solvent. After standing 30 minutes at room temperature, the solution was chilled and evaporated to dryness in the frozen state. From the residue, H.M.T., H.M.T. hydrochloride, β-chloroethylmethylethanolamine picrate (IIa) and III were isolated. No evidence was found for the presence of the dimer quaternary salts (VI–IX). It appears, therefore, that no appreciable linear dimerization occurs in aqueous solutions and that the primary action of H.M.T. upon M.B.A. is the formation of the monomeric hexamethylene tetraminium derivative.

EXPERIMENTAL

One fractionation procedure is reported here in detail for illustration.

To 1 g. of M.B.A was added 1 g. of H.M.T. and 1.5 ml. of water followed by 1.5 ml. of ethanol. The suspension cleared after stirring from 5 to 10 minutes at room temperature. After stirring for 30 minutes, 30 to 40 ml. of acetone was added and the solution chilled for several hours. A crystalline precipitate was removed by centrifugation, washed with acetone, and dried. The product, weighing 0.3–0.4 g., consisted mainly of H.M.T. which was recovered by extraction with chloroform. A small amount of insoluble material remained and was later identified as product III. No cyclic dimer of M.B.A. (XI) could be found in this fraction.

The combined acetone mother liquors were evaporated to dryness at low temperature yielding a colorless crystalline residue contaminated with a small amount of oil. Extraction with ether removed the oil which proved to be mainly β-chloroethylmethylethanolamine. This substance was recovered as the picrate from ether and the product recrystallized from hot water; yield, 0.21 g., m.p. 68–69°. *Anal.*, Cl, 9.8; picric acid, 62.3; theory: Cl, 9.7; picric acid, 62.5.

The colorless crystalline residue (insoluble in ether) was extracted several times with chloroform to remove any remaining H.M.T. Upon evaporation of the chloroform a small amount (0.1 g.) of product III was obtained; m.p. 146–149° dec. Recrystallization from cold methyl alcohol and ether raised the melting point to 152–154°.

The remaining crystalline residue (insoluble in chloroform) was dissolved in anhydrous methyl alcohol and fractionally precipitated with ether. The first crop consisted of an oily precipitate which slowly crystallized. Upon recrystallization of this material from methyl alcohol and ether, two different fractions were obtained. The first product (needles) melted at 140–143° with decomposition. *Anal.*, Cl^-, 15.0; total Cl, 23.0; theory for product VI, Cl^-, 16.3; total Cl, 24 5 There was not enough product obtained for further purification.

The second preparation which decomposed at 118–119° gave the following analyses; Cl^-, 16.5; total Cl, 16.5; N, 19.9; theory for product VII: Cl^-, 17.1; total Cl, 17.1; N, 20.2.

From the mother liquors the monomeric quaternary salt (product III) was obtained by further addition of ether. A relatively large crop of colorless feathery needles was obtained after chilling for several days. After recrystallization from methyl alcohol-ether, the product melted at 153–155° with decomposition; yield 0.7 g. *Anal.*, Cl^-, 12.3; total Cl, 23.6; N, 23.4; theory for product III: Cl^-, 12.0; total Cl, 24.0; N, 23.65. The material was subjected to further analysis for ammonia and formaldehyde. This was accomplished by hydrolysis with mineral acid followed by distillation and estimation of the formaldehyde. Ammonia was estimated in the residue by alkalinization and distillation into standard acid Found: CH_2, 27.5; NH_3—N, 15.2; theory: CH_2, 28.4; NH_3—N, 14.2. The ratio CH_2/NH_3—N was 1.8, whereas theoretically it should have been 2. For H.M.T. the ratio CH_2/NH_3—N is 1.66 ($6CH_2/4N$) whereas in hexamethylene tetraminium compounds the ratio should be 2($6CH_2/3N$). For purposes of comparison, cetylhexamethylene tetraminium iodide was prepared and similarly analyzed. Found: CH_2, 15.1; NH_3—N, 8.48; CH_2/NH_3—N, 1.8; theory: CH_2, 17.0; NH_3—N, 8.58; CH_2/NH_3—N, 2.0. These analyses support the structure assigned to the compound (III). The substance is hygroscopic and unstable; it rapidly develops a tan color unless it is kept thoroughly dry.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA]

CHEMICAL REACTIONS OF NITROGEN MUSTARD GASES.[1] II. REACTIONS WITH SECONDARY AND TERTIARY AMINES

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It has been shown in an earlier report from this laboratory (1) that hexamethylenetetramine reacts with methyl-bis(β-chloroethyl)amine (M.B.A.) to form quaternary salts. Fruton and co-workers (2, 3, 4) have made an extensive study of the relative reactivities of a number of cyclic nitrogen compounds and amino acids when mixed with M.B.A.

This report is concerned with a similar study of a number of aliphatic and cyclic amines, which was undertaken in order to determine, if possible, the relationship of molecular structure to the reactivity of these amines toward the nitrogen mustards.

The methods used were based on the thiosulfate titration procedure devised by Ogston (5) and further developed by Golumbic, Fruton, and Bergmann (6). According to these authors, the relative amounts of ethylenimine form of M.B.A. remaining, after a reaction with another reagent has occurred, can be measured by titration with sodium thiosulfate. The experiments were carried out in the following manner: to 1 ml. of M.B.A. hydrochloride (0.078 mM) in water were added 3 ml. of 0.5 *M* sodium bicarbonate and 1 ml. of an aqueous solution containing 0.29 millimoles of the test amine. In all cases the *p*H was maintained between 7.5 and 8.0. When necessary, the amine solutions were adjusted with acetic acid to *p*H 7.5–8.0 prior to mixing. The mixed solution was allowed to stand for exactly 30 minutes at room temperature and then treated with 10 ml. of 0.009 *M* sodium thiosulfate. After 10 minutes the solutions were acidified and the remaining thiosulfate titrated with a standard iodine solution. Control solutions containing M.B.A. without added test substance were simultaneously run with each series of determinations. The amount of thiosulfate which reacted during the 10-minute period furnished a measure of the ethylenimine form of M.B.A. remaining at the end of the 30 minute reaction period. This value subtracted from the control value gave the amount of M.B.A. which had reacted with the test substance. This quantity divided by the control value and multiplied by 100, gave the percentage of M.B.A. which had reacted with the test substance under these standardized conditions.

The results obtained with several cyclic amines (Table I) are in substantial agreement with those reported by Bergmann and Fruton. The competition rates of some of these substances are sufficiently high to suggest that those present in the living body would react very rapidly upon exposure to M.B.A. It

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[1] This work was done in whole under Contract No. OEM-cmr-108 between the University of Pennsylvania and the Office of Scientific Research and Development, which assumes no responsibility for the accuracy of the statements contained herein.

is noteworthy that tertiary amines are in general more reactive than secondary amines. For example, N-methylpiperidine and anserine were more reactive than piperidine and carnosine respectively.

When the aliphatic series (Table II) was studied, it became apparent that the introduction of alkyl groups larger than methyl seriously interferes with the reaction (compare triethylamine with trimethylamine).

TABLE I

Reaction of MBA with Cyclic Amines

In each experiment 0.078 millimoles MBA, 0.29 millimoles test substance and 1.5 millimoles $NaHCO_3$, in a total volume of 5 ml. was employed. The reaction time was 30 minutes.

TEST SUBSTANCE	$S_2O_3^=$ CONSUMED BY CONTROL	MBA REMAINING	MBA COMBINED WITH TEST SUBSTANCE	% REACTED
	millimoles	*millimoles*	*millimoles*	
Hexamethylenetetramine	0.060	0.010	0.050	83
Tetramethylmethylenediamine (8)	.067	.006	.061	91
Diethylenetetramethylenetetramine (9)	.066	.001	.065	99
Trimethyltrimethylenetriamine (9)	.065	.021	.044	68
Triethyltrimethylenetriamine	.065	.030	.035	54
Triisopropyltrimethylenetriamine	.065	.046	.019	29
Pyridine	.064	.037	.027	42
Nicotinic acid	.064	.043	.021	33
Nicotinamide	.064	.056	.008	13
2-Aminopyridine	.064	057	.007	11
Pyridoxine	.064	.062	.002	3
Thiamine	.066	.063	.003	5
N-Methylpiperidine	.064	.053	.011	17
Piperidine	.064	.060	.004	6
Anserine	.065	.049	.016	25
Carnosine	.065	.056	.009	14
N-Methylmorpholine	.064	.025	.039	61
Morpholine	.064	.029	.035	55
Adenylic acid	.066	.062	.004	6

Similar results were obtained when two methyl groups in triemethylamine were replaced by ethanol side chains (compare trimethylamine and methyldiethanolamine II).

I $(CH_3)_2NCH_2CH_2OH$ IV $(C_2H_5)_2NCH_2CH_2OH$

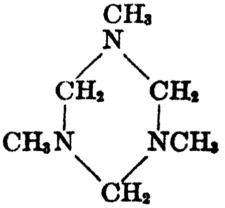
II $CH_3N(CH_2CH_2OH)_2$ V $(CH_3)_2NCH_2COOH$

III $C_2H_5N(CH_2CH_2OH)_2$ VI CH_3NHCH_2COOH

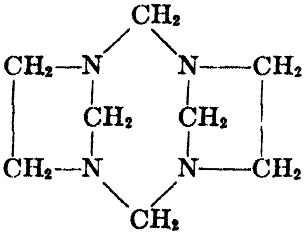
Compounds III and IV were still less reactive. The introduction of one ethanol group in place of a methyl did not affect the reaction with M.B.A. Thus dimethylaminoethanol I was fully as effective as trimethylamine. Furthermore, the replacement of one ethanol or methyl group by an acetic acid residue did not inhibit the reaction. Dimethylglycine (V) proved to be as reactive as dimethylaminoethanol (I) or trimethylamine. That tertiary nitrogen is more reactive than secondary nitrogen, was again indicated by the more complete reaction obtained with dimethylglycine (V) as compared with sarcosine (VI).

This information suggested the synthesis and study of a number of other compounds which it was hoped would prove to be more reactive. Among them were tetramethylmethylenediamine (VII), trimethyltrimethylenetriamine (VIII), and diethylenetetramethylenetetramine, which was prepared from ethylenediamine and formaldehyde (7), and to which has been assigned the tentative structure IX.

VII $(CH_3)_2NCH_2N(CH_3)_2$



VIII



IX

TABLE II

REACTION OF MBA WITH ACYCLIC AMINES

All concentrations and experimental conditions were maintained as described in Table I.

TEST SUBSTANCE	$S_2O_3^{=}$ CONSUMED BY CONTROL	MBA REMAINING	MBA COMBINED WITH TEST SUBSTANCE	% REACTED
	millimoles	*millimoles*	*millimoles*	
Trimethylamine	0.064	0.023	0.041	64
Triethylamine	.062	.057	.005	8
Dimethylamine	.064	.053	.011	17
Ethyldiethanolamine	.064	.061	.003	5
Diethylaminoethanol	.064	.061	.003	5
Methyldiethanolamine	.064	.044	.020	31
Dimethylaminoethanol	.064	.021	.043	67
Dimethylglycine (10)	.064	.024	.040	63
Sarcosine	.064	.048	.016	25
Methylenediglycine (11)	.065	.028	.037	57

Compounds VII and IX proved to be more reactive than H.M.T. (Table I). Trimethyltrimethylenetriamine (VIII) although somewhat less active was significantly more effective than its corresponding ethyl and isopropyl homologs (triethyl- and triisopropyl-trimethylenetriamine).

Several of these substances were tested similarly with other nitrogen mustards, namely ethyl-bis(β-chloroethyl)amine (EBA) and tris(β-chloroethyl)amine (TBA) and were found to react at about the same rate under similar conditions (Table III).

The data indicate that amines will react rapidly with the nitrogen mustards when the following conditions are fulfilled:

1. The nitrogen must be tertiary. 2. In the aliphatic series, the replacement of methyl groups by ethyl or larger alkyl radicals diminishes the reactivity. 3. Although one ethanol or acetic acid side chain may be substituted for a methyl group, further introduction of larger groups impairs the activity. 4. The nitrogen in cyclic amines appears to be somewhat more reactive than that of aliphatic amines. Substances containing two or more ethyl groups (or larger radicals) attached to nitrogen will react efficiently only if the substance is cyclic. 5. The most effective reagents appear to be those substances containing two or more tertiary nitrogen atoms separated by methylene groups.

TABLE III

REACTIVITY OF TRIS(β-CHLOROETHYL)AMINE AND ETHYL-BIS(β-CHLOROETHYL)AMINE

All concentrations and experimental conditions were maintained as described in Table I.

TEST SUBSTANCE	N-MUSTARD EMPLOYED	$S_2O_3^=$ CONSUMED BY CONTROL	N-MUSTARD REMAINING	N-MUSTARD COMBINED WITH TEST SUBSTANCE	% REACTED
		millimoles	*millimoles*	*millimoles*	
Hexamethylenetetramine	TBA	0.074	0.017	0.057	77
	EBA	.076	.017	.059	78
Trimethyltrimethylenetriamine	TBA	.070	.023	.047	67
	EBA	.076	.020	.056	74
Diethylenetetramethylenetetramine	TBA	.077	.014	.063	82
	EBA	.077	.001	.076	99

PHILADELPHIA, PA.

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[Contribution from the Cobb Chemical Laboratory of the University of Virginia]

ANTIMALARIALS. α-PHENYL-β-DIALKYLAMINO ALCOHOLS[1]

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This investigation had its beginning in the fall of 1942 as a part of the cooperative effort initiated by the Division of Chemotherapy of the National Institute of Health under Dr. L. F. Small (1) and it was continued into the summer of 1944 at which time, although not completed, it was interrupted because of the greater promise and urgency of other problems. It was based on convincing evidence that the α-aryl-β-*tert.*-amino alcohol system is the structural feature of quinine which is chiefly responsible for its antimalarial activity; it had been shown that the quinuclidine ring system is not essential for this activity and can be replaced by non-cyclic secondary or tertiary amino groups, and also that the quinoline nucleus is not essential and can be replaced by other aryl nuclei such as the naphthyl and tetrahydrophenanthryl (*cf.* 1, 2, 3, 4, 5).

The first compounds made of the α-phenyl-β-dialkylaminoethanol type (IA) carried the following as the benzenoid groups: *p*-isopropylphenyl, carvacryl, *p*-cyclohexylphenyl, *p*-benzylphenyl, and *p*-bibenzyl. These compounds were made in order to test the effectiveness of the simple phenyl nucleus when it was so weighted with substituents as to bring the molecular weight to a level comparable with that of quinine and other active drugs.

The first compound found which possessed significant antimalarial activity was α-4-chlorophenyl-β-diamylaminoethanol (IIAd).[4] The dioctylamino analog (IIAh) which was made later showed still higher activity. These compounds had been made with two points in mind, one, the possible activating influence of the *p*-chlorine, and the other, the partial compensation for the low molecular weight of the nucleus (as compared with that of quinine and Atabrine) by the use of this nuclear substituent and by the use of the long-chain N,N-dialkyl groups. The activity of these compounds was on the order of one-quarter of that of quinine and this finding, surprising at the time, stimulated the extensive investigation of a large variety of analogs to evaluate the effect of (a) the phenyl nucleus itself; (b) as many variations as possible in the alkyl groups on nitrogen; (c) the variation in nuclear halogen from fluorine, chlorine, and bromine to iodine; (d) the substitution of other groups, notably alkyl and alkoxyl; (e) the relative effect of the ortho, meta, and para positions of the substituent, especially the ortho and para where the electron displacements are similar in a degree to that in quinine; (f) the insertion of two or more substituents, including alkyls and alkoxyls, in as many different arrangements as could quickly be produced from easily accessible materials; (g) the lengthening of the amino alcohol chain, $—\underset{\mathrm{OH}}{\mathrm{CH}}—\underset{\mathrm{NR_2}}{\mathrm{CH}}—(\mathrm{CH_2})_n\mathrm{CH_3}$, where n = 0, 1, 3, and 9; and (h) the separation of the alcoholic hydroxyl and dialkylamino group by one extra carbon, involving the type, $—\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CH_2CH_2NR_2}$. The work covered fifty different nuclear variations and over sixty variations in the N,N-dialkyl groups; and it involved the preparation of a total of 184 amino alcohols which are listed in Table I (6), together with fifty-five amino ketones (also listed in Table I) which were isolated for purposes of comparison.

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[1] The larger portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

The completion of the manuscript and a few of the experiments and analyses were carried out with assistance from a grant-in-aid from the National Institute of Health to the University of Virginia.

[2] Present addresses: [a]Southern Research Institute, Birmingham, Ala.; [b]University of Texas, Austin, Texas; [c]Birmingham-Southern College, Birmingham, Ala.; [d]National Institute of Health, Bethesda Md.; [e]Heyden Chemical Corp., Fords, N. J.; [f]Rohm and Haas, Phila., Penna.; [g]Chemical Abstracts, Ohio State Univ., Columbus, O.; [h]Tennessee Eastman Co., Rochester, N. Y.; [i]Medical College of Virginia, Richmond, Va.; [j]Smith, Kline and French Laboratories, Phila., Penna.

[3] Assisted by Philip Francis duPont Fellowships, 1942–1944.

[4] Submitted for testing February 13, 1943.

RESULTS OF ANTIMALARIAL TESTS

It is clear from the quinine equivalents listed in Table I that a considerable proportion of the many types of α-phenyl-β-amino alcohols and the corresponding ketones are moderately or slightly active against avian malaria. The series most extensively explored was the *p*-chlorophenyl, and here, with one outstanding exception, most of the dialkylamino and benzylalkylamino alcohols within certain ranges of molecular weight showed consistent antimalarial activity of a modest order ranging from below one-tenth to one-quarter of that of quinine. The exception was the diisooctylamino compound (di-2-ethylhexyl) (IIAi) which proved to be inactive in contrast to the moderately active di-*n*-octylamino isomer (IIAh).

Little indication appeared of any significant or striking group-positional effect upon the activity, and it is noteworthy that, in spite of the steric hindrance involved, α-2,6-dichlorophenyl-β-dioctylaminoethanol (XXIX) was moderately active.

The activities of the amino ketones tested in most cases were of the same order of magnitude as those of the corresponding amino alcohols.

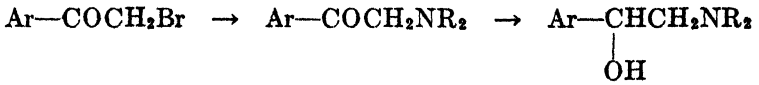
With a few exceptions in a long list of examples the amino alcohols and ketones based on morpholine and on piperidine proved to be inactive.

It was only toward the end of this program of research, with the benefit of experience and knowledge in the matter of the favorable balance of nuclear substituents and molecular weight as modified by N,N-dialkyl groups, that the most active drugs were found.

Special mention should be made of the following α-phenyl-β-dioctylaminoethanols, each of which proved to be equal to or better than quinine in at least one test against avian malaria; namely, those with the nuclear substitutions: 3,4-dichloro (XXV), 2,4-dichloro (XXVI), 2,5-dichloro (XXVII), 2-methyl-4,5-dichloro (XXXIV), and 4-*n*-hexyl (XIII). It is along these lines of substitution in the nucleus, and others suggested by the results described in this paper, that some further work is now being undertaken in order to find the upper limits of antimalarial activity which may be possible in this type of compound.

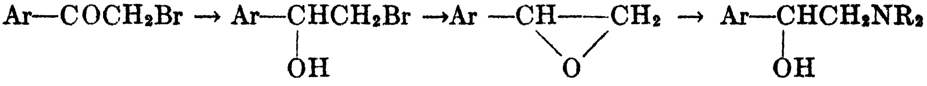
SYNTHETIC METHODS

Most of the drugs were made by the following transformations: condensation of the bromomethyl ketone with the appropriate secondary amine to give the *tert.*-aminomethyl ketone, and reduction by means of aluminum isopropoxide to the amino alcohol (8).[4]



$$\text{Ar—COCH}_2\text{Br} \rightarrow \text{Ar—COCH}_2\text{NR}_2 \rightarrow \text{Ar—}\underset{\text{OH}}{\underset{|}{\text{C}}}\text{HCH}_2\text{NR}_2$$

An alternative path, used in a few cases only, was reduction of the bromomethyl ketone to the bromohydrin and condensation of this with the appropriate secondary amine (8, 9, 10).



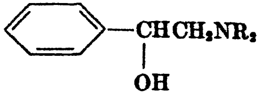
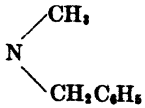
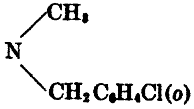
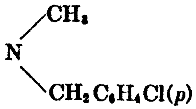
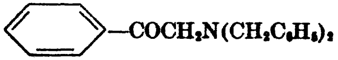
$$\text{Ar—COCH}_2\text{Br} \rightarrow \text{Ar—}\underset{\text{OH}}{\underset{|}{\text{C}}}\text{HCH}_2\text{Br} \rightarrow \text{Ar —}\underset{\diagdown\,\text{O}\,\diagup}{\text{CH——CH}_2} \rightarrow \text{Ar—}\underset{\text{OH}}{\underset{|}{\text{C}}}\text{HCH}_2\text{NR}_2$$

Those bromomethyl ketones which were not available as starting materials were for the most part made by bromination of the methyl ketones in ether as the solvent, but in a few cases they were made from the acids *via* the now widely used path through the acid chloride and the diazomethyl ketone (5). The methyl ketones, when not available, were usually made from the substituted aromatic hydrocarbons by the Friedel-Crafts reaction; a few were made through the addition of methylmagnesium iodide to the appropriate nitrile; and one was made from the aldehyde by addition of methylmagnesium iodide and oxidation of the resulting alcohol to the ketone.

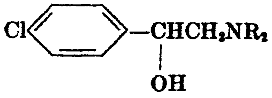
Much of the work here reported was done before the efficacy of the synthetic path through the bromohydrin was realized, and doubtless the yields in many of these syntheses could be greatly improved by the use of the latter procedure. Throughout this investigation the governing objective was to prepare as wide a variety as possible of new types of drugs in sufficient quantity and purity for adequate screening tests, and to prepare them as quickly as possible; consequently, once samples were tested and found to be without further interest, no more work was done on preparative details, derivatives, and intermediates, nor toward securing other data normally desirable for recording. Many short cuts in syntheses were taken and the isolation of intermediates often was omitted for the sake of the saving of time. The necessarily limited data accumulated

TABLE I

THE α-PHENYL-β-DIALKYLAMINO ALCOHOLS AND CORRESPONDING KETONES

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{25°}$	B.P. OR M.P., °C.[f]
IA							
a	4666	N(*n*-octyl)$_2$	<0.06	5R;3K	13	1.4830	200–203/1 mm.
b	8346	N(*n*-nonyl)$_2$	0.06	5R;4K	26	1.4847	225–227/4 mm.
c	8118		<0.06	6R;3L	7[n,i]	1.5610–1.5613	171–173/1 mm.
d	8889		<0.1	5R;3K	—	1.5675$^{25°}$	167–168/2 mm.
e	8413		<0.1	5R;3K	28	1.5690–1.5693	187–190/2 mm.
f	6749	N($CH_2C_6H_5$)$_2$·HCl	<0.03	8UW;3N	65	abs. EtOH-*i*PrOH[j]	213
IB							
	6548		—[w]	Ref. 13	71	ethanol	80–82[w]

IIA



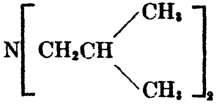
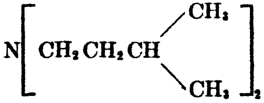
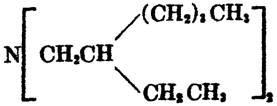
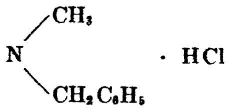
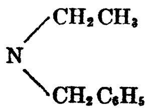
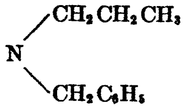
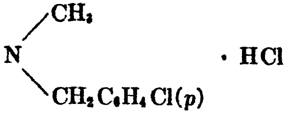
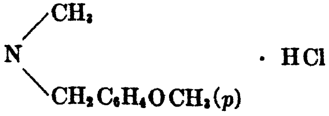
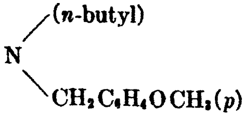
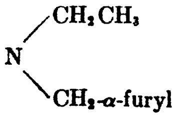
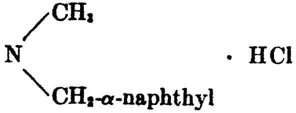
a	9517	$N(CH_2CH_3)_2$	<0.1	7R;3M	53	1.5190	117–119/2 mm.
b	4914	$N(CH_2CH_2CH_2CH_3)_2$	sl.act.^{b_3}	5TR;3K	38	1.5026$^{24°}$	162–165/2 mm.
b_1	—	b-hydrochloride	—	Q	—	—	98–99
c	7210		<0.06	7R;3FM	67	1.5021	166–167/1 mm.
d	3097	$N(CH_2CH_2CH_2CH_2CH_3)_2$	0.3	5TR;4K	59	1.4990	160–162/2 mm.
e	8475		0.1	5TR;4K	51	1.4979–1.4980	160–162/3 mm.
f	6418	N(*n*-hexyl)$_2$	<0.3	9R;3K	36	1.4951$^{28°}$	170–171/1 mm.
g	8302	N(*n*-heptyl)$_2$·HCl	<0.06	5RQ;4K	20	ethyl acetate	87–88
h	4067	N(*n*-octyl)$_2$	1.0/ (0.3)^{b_1}	11R;5R	52^{k}	1.4941$^{25°}$	222/2 mm.
h_1	—	h-hydrochloride	—	5RQ;3K	—^{k}	EtOH-H$_2$O	86–87
i	5419		<0.03	5R;3K	65	1.4960	184–189/2 mm.

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA $-NR_2$	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{20°}$	B.P. OR M.P., °C.[f]
j	7485	N(*n*-nonyl)$_2$	0.1	7R;4M	18	1.4912–1.4914	216–218/2 mm.
k	8290	N(*n*-decyl)$_2$	0.1	5R;4K	37	1.4898–1.4900	245–246/1.8 mm.
l	8133	N(*n*-undecyl)$_2$	<0.03	5R;3K	43	1.4899–1.4902	228–230/2 mm.
l$_1$	—	l-hydrochloride	—	Q	—	ethyl acetate	86–88
m	9019	N(*n*-dodecyl)$_2$	<0.03	5S;3K	—[k]	1.4881–1.4900	—[k]
m$_1$	—	m-hydrochloride	—	Q	—	—	79–82[m]
n	8826	N(*n*-tridecyl)$_2$	<0.03	5S;3K	20	1.4872–1.4880	—[k]
o	4915	 $N(CH_3)(CH_2C_6H_5) \cdot HCl$	0.06	5TR;3K	54	abs. ethanol	166–167
p	8296	 $N(CH_2CH_3)(CH_2C_6H_5)$	0.06	7R;3M	38	isopropyl ether	57–58[e]
q	6754	 $N(CH_2CH_2CH_3)(CH_2C_6H_5)$	0.06	5S;4K	58	ethanol	44–45

r	8299	$N\begin{matrix}/CH(CH_3)_2\\ \backslash CH_2C_6H_5\end{matrix}$	0.03	6U;4L	56	ethanol	65–67
r_1	—	r-hydrochloride	—	W	—	isopropanol	185–186
s	5044	$N\begin{matrix}/CH_2CH_2CH_2CH_3\\ \backslash CH_2C_6H_5\end{matrix}$	0.06	5R;3K	—	ethanol	49–50[e]
t	8301	$N\begin{matrix}/CH(CH_3)CH_2CH_3\\ \backslash CH_2C_6H_5\end{matrix} \cdot HCl$	0.06	6Q;3GL	44	acetone	176–179
u	8128	$N\begin{matrix}/(n\text{-amyl})\\ \backslash CH_2C_6H_5\end{matrix}$	0.1	5R;3K	30	$1.5424^{26°}$	209–212/2 mm.[e]
v	7983	$N\begin{matrix}/(n\text{-dodecyl})\\ \backslash CH_2C_6H_5\end{matrix}$	0.03+	5R;4K	47	—[k]	56–57
w	8382	$N\begin{matrix}/\text{cyclohexyl}\\ \backslash CH_2C_6H_5\end{matrix} \cdot HCl$	<0.15	6Q;3L	15	butanone	190–192 dec.
x	6747	$N\begin{matrix}/CH_3\\ \backslash CH(C_6H_5)CH_2(CH_2)_2CH_3\end{matrix}$	<0.06	5R;4K	49	1.5512	197–198/1 mm.

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA $-NR_2$	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n^{25}_{D}	B.P. OR M.P., °C[f]
y	6974	 $N(CH_3)(CH_2C_6H_4Cl(p)) \cdot HCl$	0.06	7RQ;3G	53	acetone	161–162
z	8477	 $N(CH_3)(CH_2C_6H_4OCH_3(p)) \cdot HCl$	0.06	5Q;3K	66	1:10-EtOH-EtOAc	150–152
aa	8479	 $N(n\text{-butyl})(CH_2C_6H_4OCH_3(p))$	0.06	6TU;3L	39	75% ethanol	55[e]
bb	—	$N(CH_2C_6H_5)_2$	—	—	—	70% ethanol	97–98
bb₁	5050	bb-hydrochloride	0.3	9TQ;3K	55	CH_3OH-ether	200.5–202
cc	8181	 $N(CH_2CH_3)(CH_2\text{-}\alpha\text{-furyl})$	<0.06	7R;3GM	32	1.5423	176/10 mm.
dd	9018	 $N(CH_3)(CH_2\text{-}\alpha\text{-naphthyl}) \cdot HCl$	<0.04	6Q;3L	—	isopropanol	189–190

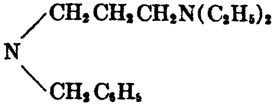
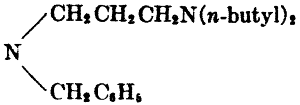
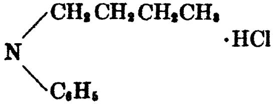
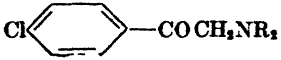
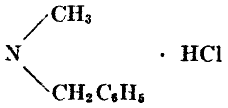
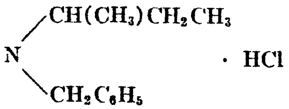
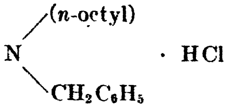
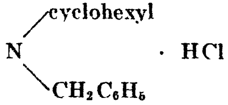
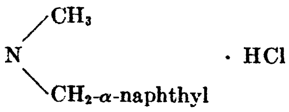
ee	7389	 $\mathrm{N}\begin{cases}CH_2CH_2CH_2N(C_2H_5)_2\\ CH_2C_6H_5\end{cases}$	<0.3	5R;4K	17	1.5453	219–221/4 mm.
ff	8982	 $\mathrm{N}\begin{cases}CH_2CH_2CH_2N(n\text{-butyl})_2\\ CH_2C_6H_5\end{cases}$	<0.1	5R;4K	28	1.5354–1.5360	241–243/1 mm.
gg	—	tetrahydroisoquinolyl	—	—[k]	—[k]	pet. ether	90.5–91
gg₁	4912	gg-hydrochloride	<0.06	—[k]	—[k]	water	229–231[e]
hh	4913	tetrahydroquinolyl	<0.1	8TR;3FN	28	$1.6121^{29°}$	223–227/3 mm.
ii	7981	morpholinyl	<0.1	8TU;3GN	79	ligr.-*i*PrOH	78–80
jj	7198	2-methylmorpholinyl[m]	<0.1	6T;3GL	31	ligroin	86–87
kk	7197	2,6-dimethylmorpholinyl	<0.06	6R;3GL	25	$1.5292^{25°}$	169–170/1 mm.
ll	8849	2-(*n*-hexyl)piperidyl	<0.1	11R	53	1.5248–1.5249	150–169/2 mm.
mm	7517	*trans*-dodecahydrocarbazyl	<0.1	7TR;3M	47	80% ethanol[h]	81–82
nn	8398	 $\mathrm{N}\begin{cases}CH_2CH_2CH_2CH_3\\ C_6H_5\end{cases}\cdot HCl$	<0.02	6Q;3GL	12	acetone-ether	145–146 dec.
IIB							

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA $-NR_2$	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{20°}$	B.P. OR M.P., °C.[f]
a	—	$N(CH_2CH_3)_2 \cdot HCl$	—	3FL	—	ethanol-ether	158–159[e]
b	6645	 $N(CH_3)(CH_2C_6H_5) \cdot HCl$	0.06	3L	60	butanone	188–191
c	—	 $N(CH(CH_3)CH_2CH_3)(CH_2C_6H_5) \cdot HCl$	—	3GL	60	*i*PrOH-butanone	167–170
d	7398	 $N(n\text{-octyl})(CH_2C_6H_5) \cdot HCl$	0.02	3FL	—	EtOAc-ethanol	167–169[m]
e	—	 $N(\text{cyclohexyl})(CH_2C_6H_5) \cdot HCl$	—	3L	44	acetone	185–186 dec.
f	—	 $N(CH_3)(CH_2\text{-}\alpha\text{-naphthyl}) \cdot HCl$	—	4L	60	ethanol	202–203
g	6644	tetrahydroisoquinolyl	<0.06	3FN	63	ethanol	100[e]
h	—	morpholinyl	—	—	—	ligroin	79–80[m]

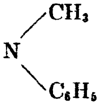
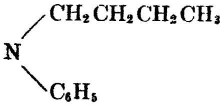
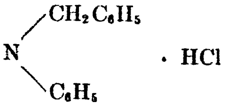
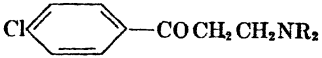
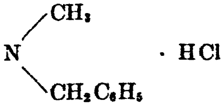
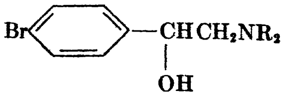
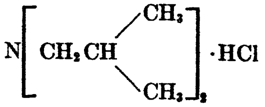
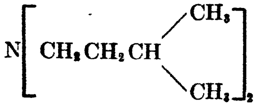
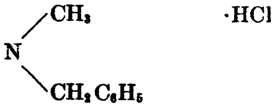
h_1	6641	h-hydrochloride	<0.1	3GL	59	ethanol	227–228 dec.
i	7387	2-methylmorpholinyl·HCl	<0.06	3GL	77	isopropanol	208–210 dec.
j	6640	2,6-dimethylmorpholinyl ·HCl	<0.06	3GL	41	isopropanol	219–221 dec.
k	6661	 $N(CH_3)(C_6H_5)$	<0.03	Ref. 7	36	ethanol	109–110
l	6667	 $N(CH_2CH_2CH_2CH_3)(C_6H_5)$	<0.03	3N	50	ethanol	85–86^{u}
m	8127	 $N(CH_2C_6H_5)(C_6H_5)\cdot HCl$	<0.02	3NP	62	isopropanol	163–164
n	—	tetrahydroquinolyl	—	3FN	55	ethanol	106–108
IIC							
a	—	N(n-amyl)$_2$·HCl	—	—^{k}	67^{n}	acetone-ether	100–103
b	7393	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	<0.06	—^{k}	63^{n}	ethanol	170–172

TABLE I *con't.*

NO	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{20°}$	B.P. OR M.P., °C.[f]
IIIA							
a	7205	 $N[CH_2CH(CH_3)_2]_2 \cdot HCl$	<0.03	5Q;3K	25	acetone-ether	142.5
b	4911	$N(CH_2CH_2CH_2CH_2CH_3)_2$	0.3	5TR;4K	52	1.5120	166/2 mm.
c	8933	 $N[CH_2CH_2CH(CH_3)_2]_2$	0.1	5TR;4K	65	1.5091-1.5092	155-157/2 mm.
d	8396	N(*n*-hexyl)$_2$	<0.3	5TS;3K	40	1.5069-1.5073	180-181/1 mm.
e	8300	N(*n*-heptyl)$_2$·HCl	<0.15	5Q;4K	62	ethyl acetate	96.4
f	8367	N(*n*-octyl)$_2$	0.06	5TR;3K	14	1.4991-1.4992	210-212/1 mm.
g	7112	N(*n*-nonyl)$_2$	0.3	7R;3M	45	1.4990	235-239/1 mm.
h	7204	 $N(CH_3)(CH_2C_6H_5) \cdot HCl$	0.06	6Q;3L	60	ethanol-ether	175-176

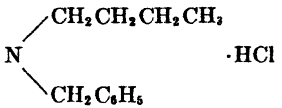
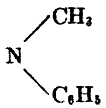
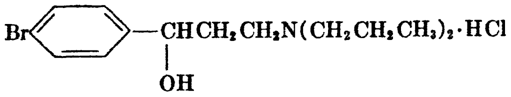
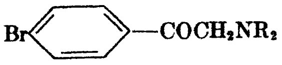
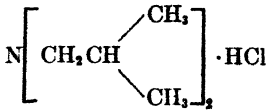
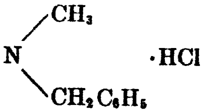
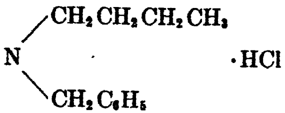
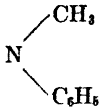
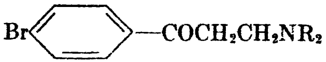
i	8397	 $N(CH_2CH_2CH_2CH_3)(CH_2C_6H_5)\cdot HCl$	0.15	5Q;3K	39	ethyl acetate	125–127
j	7196	morpholinyl	<0.06	8TU;3GN	50	ligroin	87.5–88.5
k	7980	2-methylmorpholinyl[m]	<0.06	6U;3GL	29	ligroin	94–95
l	8132	2-ethylmorpholinyl·HCl	<0.06	6TQ;3GL	52	CH_3OH-*i*PrOH	186–187
m	8130	3-ethylmorpholinyl·HCl	<0.06	7TUQ;3GM	33	acetone	141–143
n	7979	2,6-dimethylmorpholinyl·HCl	<0.06	6RQ;3GL	35	isopropanol	193 dec.
o	8131	3,3-dimethylmorpholinyl·HCl	<0.06	8T;3N	43	ethanol	241–242 dec.
p	7917	*trans*-decahydroquinolyl·HCl	<0.06	8T;4N	56	isopropanol	234–236[e]
q	—	 $N(CH_3)(C_6H_5)$	—	8R;3N	33	1.6135	195–197/3 mm.
IIIB							
	—		—	—[k]	—[i]	acetone	162–164
IIIC							

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA $-NR_2$	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{20°}$[e]	B.P. OR M.P., °C.[f]
a	7206	 $N[CH_2CH(CH_3)_2]_2 \cdot HCl$	<0.03	3L	29	ethyl acetate	139–140[u,w]
b	6643	 $N(CH_3)(CH_2C_6H_5) \cdot HCl$	0.06	3L	71	ethanol-ether	190–191
c	7397	 $N(CH_2CH_2CH_2CH_3)(CH_2C_6H_5) \cdot HCl$	0.06	3L	20	*i*PrOH-ether	166
d	—	morpholinyl	—	Ref. 19	78	isopropanol	91–92
d_1	7391	d-hydrochloride	<0.1	Ref. 19	52	ethanol	223–224 dec.
e	7390	2-methylmorpholinyl·HCl	<0.15	3GL	66	1:6-CH_3OH-*i*PrOH	231–232 dec.[v]
f	—	2-ethylmorpholinyl·HCl	—	3GL	82	ethanol	228 dec.[v]
g	7978	2,6-dimethylmorpholinyl·HCl	<0.06	3GL	58	isopropanol	235–236 dec.[v]
h	—	3,3-dimethylmorpholinyl	—	3N	49	isopropanol	73–74[u,w]
h_1	—	h-hydrochloride	—	3P	—	ethanol	232 dec.[v]

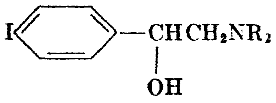
i	6545	*trans*-decahydroquinolyl	<0.1	4N	77	88% ethanol	77.5-78
j	7258	 $N(CH_3)(C_6H_5)$	<0.03	3N	36	ethanol	105-106

IIID



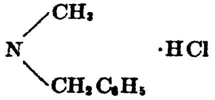
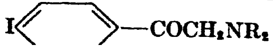
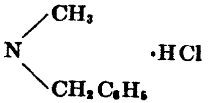
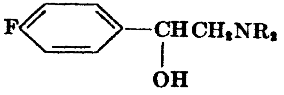
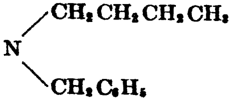
a	13361	$N(n\text{-propyl})_2 \cdot HCl$	<0.06	—[k]	55[n]	*i*PrOH-ether	128-130
b	8981	$N(n\text{-butyl})_2 \cdot HCl$	0.06	—[k]	30[n]	*i*PrOH-ether	133-135

IVA

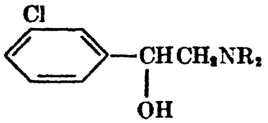


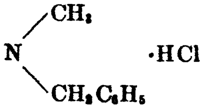
a	7203	$N(ethyl)_2 \cdot HCl$	0.06	6Q;3L	—[i]	EtOH-ether	181-184
b	7201	$N(n\text{-propyl})_2 \cdot HCl$	sl.act.[b,z]	6Q;3L	—[i]	EtOH-ether	196-197
c	7200	$N(n\text{-butyl})_2 \cdot HCl$	0.15	6Q;3L	—[i]	EtOH-ether	134-136
d	8184	$NH\text{-}n\text{-butyl} \cdot HCl$	0.3	6Q;3L	65	EtOH-ether	183-186
e	5030	$N(n\text{-amyl})_2 \cdot HCl$	<0.3	7Q;3M	35	$CHCl_3$-ether	99.5-101
f	—	$N(n\text{-octyl})_2$	—	7R;3M	38	1.5136_{30}°	230-236/1 mm.[a]
f_1	9514	f-hydrochloride	0.2	Q	—	EtOAc-pet.ether	91-93

TABLE I *con't.*

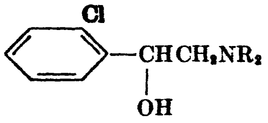
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{25}[e]	B.P. OR M.P., °C.[f]
g	7199	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	<0.06	6Q;3L	—[i]	EtOH-ether	185–187
h	7202	piperidyl·HCl	<0.06	6Q;3L	—[i]	EtOH-ether	249–251
IVB		 $I-C_6H_4-COCH_2NR_2$					
a	7395	N(*n*-propyl)$_2$·HCl	0.06	3L	89	EtOH-ether	180–186[g]
b	7394	N(*n*-butyl)$_2$·HCl	0.06	3L	82	EtOH-ether	207–208 dec.
c	6642	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	0.03	3L	77	EtOH-ether	209–211[g]
d	7396	piperidyl·HCl	<0.06	3L	55	EtOH-ether	250–251 dec.
V		 $F-C_6H_4-CH(OH)CH_2NR_2$					
a	7212	N(*n*-octyl)$_2$	0.06	5R;3K	56	1.4780	196/1 mm.
b	8414	N(*n*-nonyl)$_2$	0.1	5R;3K	37	1.4780	232–233/1 mm.
c	7211	 $N(CH_2CH_2CH_2CH_3)(CH_2C_6H_5)$	0.06	5R;3K	66	1.5305	173.5/1 mm.

VI



a	8125	$N(n\text{-octyl})_2$	0.1	5S;3K	22[n]	1.4958	238–242/10 mm.
b	8122	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	0.15	6Q;3L	26[n]	acetone	159–160

VII



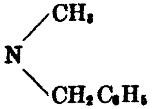
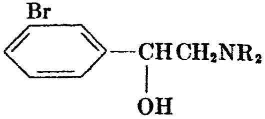
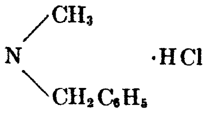
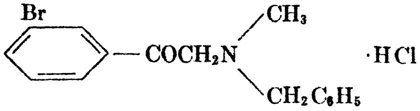
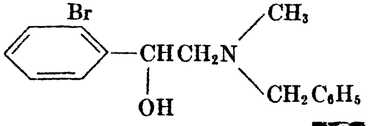
a	—	$N(n\text{-amyl})_2$	—	5R;3K	53	1.5000	160–171/0.5 mm.[a]
a_1	6755	a-hydrochloride	<0.15	Q	40	EtOH-ether	92–93.5
b	6748	$N(n\text{-octyl})_2$	0.1	5R;3K	43	1.4928	218–219/2 mm.
c	—	 $N(CH_3)(CH_2C_6H_5)$	—	5R;3K	72	1.5692	163–164/1 mm.[a]
c_1	8126	c-hydrochloride	0.06	Q	63	EtOH-ether	127–129

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20e}	B.P. OR M.P., °C.[f]
VIIIA							
a	8498	N(*n*-butyl)$_2$·HCl	0.15	5RQ;3K	—	EtOH-ether	146
b	8124	N(*n*-amyl)$_2$	0.1	5R;3K	30	1.5138	178–180/4 mm.
c	8123	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	0.15	6Q;3L	36	*i*PrOH-ether	181
VIIIB							
	—		—	3L	60	ethanol	200
IX							
	8939		<0.1	7R;3M	59	1.5826–1.5839	172–175/2 mm.

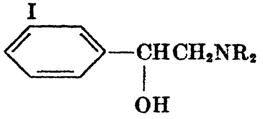
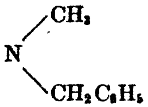
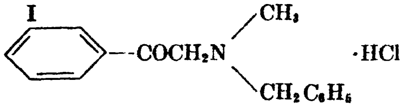
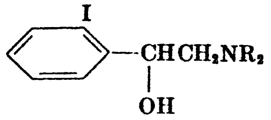
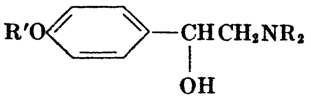
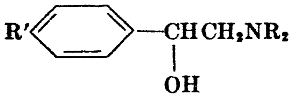
XA							
a	9040	$N(CH_3)_2$	0.04	5R;3K[p]	26	1.5872	132–133/2 mm.
b	—	$N(ethyl)_2$	—	7R;3M	68	1.5661	149.5/3 mm.[u]
b_1	8499	b-hydrochloride	0.15	Q	43	EtOH-ether	105–108
c	—	N(*n*-propyl)$_2$	—	7R;3M	56	1.5502	166–167/3 mm.[u]
c_1	8183	c-hydrochloride	0.15	Q	49	EtOH-ether	130–133
d	—	N(*n*-butyl)$_2$	—	7R;3M	58	1.5399	190/4 mm.[u]
d_1	8182	d-hydrochloride	0.15	Q	48	EtOH-ether	127–128
e	—	 $N(CH_3)(CH_2C_6H_5)$	—	6R;3L	56	1.6075	195/2 mm.[u]
e_1	9042	e-hydrochloride	0.06	Q	45	EtOH-ether	173–176
XB							
	8347		0.06	3L	97	EtOH-ether	199–204

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
XI							
a	9038	$N(ethyl)_2 \cdot HCl$	0.1	7RQ;3M	26	EtOH-ether	171–174[e]
b	9024	$N(n\text{-propyl})_2 \cdot HCl$	<0.15	5RQ;3K	23	EtOH-ether	143–145
c	9022	$N(n\text{-butyl})_2 \cdot HCl$	<0.06	5RQ;3K	20	EtOH-ether	117–120[e]
d	9026	$N(CH_3)(CH_2C_6H_5) \cdot HCl$	0.04	7SQ;3M	25[k]	EtOH-ether	156–159
XII			(a) R′ = —CH_3; (b) R′ = —CH_2CH_3; (c) R′ = —$CH_2CH_2CH_2CH_3$				
a	2585	$N(n\text{-amyl})_2$	<0.3	5TS;3K	30[n]	1.4958	182–191/2 mm.
b	3103	$N(n\text{-amyl})_2$	<0.3	5TR;3K	25[n]	1.4953	202–206/2 mm.
c	3104	$N(n\text{-butyl})_2$	<0.3	5TR;3K	20[n]	1.4950	200–205/2 mm.
XIII			(a,b) R′ = isopropyl; (c,d) R′ = *n*-hexyl; (e,f) R′ = cyclohexyl; (g) R′ = *n*-decyl; (h) R′ = *n*-dodecyl.				

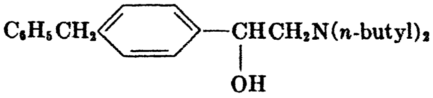
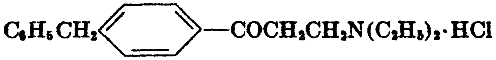
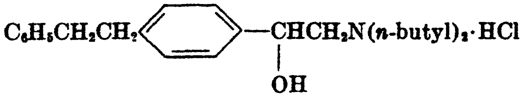
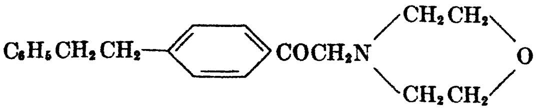
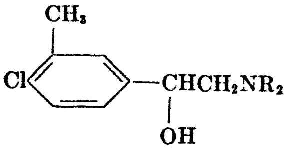
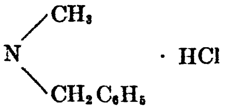
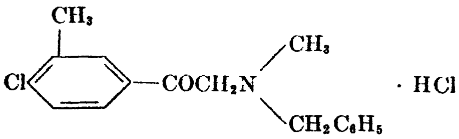
a	2586	N(n-butyl)$_2$	<0.3	5R;4K	24^n	1.4964	214–215/14 mm.
b	3108	N(n-amyl)$_2$	<0.1	5R;4K	26^n	—	206/4 mm.
c	8842	N(n-amyl)$_2$	0.04	5S;4K	39^n	1.4897	$—^k$
d	8838	N(n-octyl)$_2$	0.3 $(2.0)^{b_2}$	5R;4K	34^n	1.4867	245–258/ 2. mm
e	3550	N(ethyl)$_2$	<0.3	5R;4K	34^n	EtOH-H$_2$O	59–60
f	3109	N(n-butyl)$_2$	<0.1	5R;4K	41^n	—	229–230/6 mm.
g	8839	N(n-butyl)$_2$	<0.3	5S;4K	14^n	1.4894	$—^k$
h	9830	N(ethyl)$_2$	<0.6	5S;4K	31^n	1.4962	200–220/2 mm.
XIVA		 $C_6H_5CH_2C_6H_4CH(OH)CH_2N(n\text{-butyl})_2$					
	2747		<0.3	5R, 3G	9^n	1.5340	217–218/2 mm.
XIVB		 $C_6H_5CH_2C_6H_4COCH_2CH_2N(C_2H_5)_2\cdot HCl$					
	—		—	$—^k$	34^n	CHCl$_3$-ether	$105–106.5^l$
XVA		 $C_6H_5CH_2CH_2C_6H_4CH(OH)CH_2N(n\text{-butyl})_2\cdot HCl$					
	3542		<0.3	$5Q;3F^k$	40^k	EtOAc or H$_2$O	118.5–119

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR₂	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
XVB							
	3546		<0.06	3N	57	ethanol	119–120
XVIA							
a	6656	N(*n*-amyl)₂	<0.3	—[k]	36	$1.5040^{24°}$	196–200/2–3 mm.
b	7208	N(*n*-octyl)₂	0.06	5R;3K	13[n]	1.5051–1.5061	216–221/0.5 mm.
c	7207	 $N(CH_3)(CH_2C_6H_5) \cdot HCl$	<0.06	6Q;3L	18[i,n]	abs. EtOH-ether	188–189
XVIB							
	7392		0.06	3L	24[n]	abs. EtOH-ether	196–197

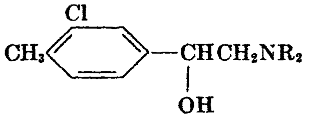
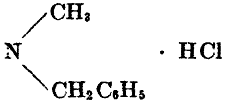
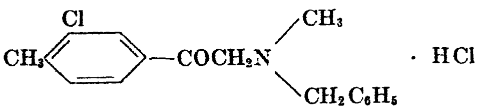
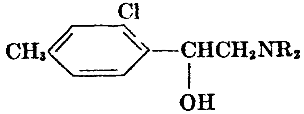
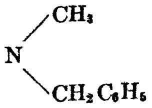
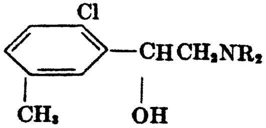
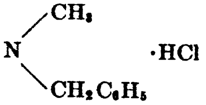
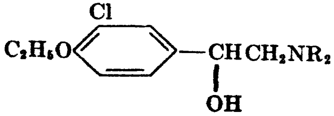
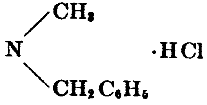
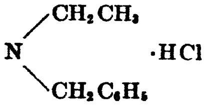
XVIIA							
a	8860	N(*n*-amyl)$_2$	<0.1	7R;3M	30[n]	1.5047	175–177/1 mm.
b	8895	N(*n*-octyl)$_2$	0.3	7R;3M	34[n]	1.5065	210–215/1 mm.
c	8892	 $N(CH_3)(CH_2C_6H_5) \cdot HCl$	<0.02	6Q;3L	37[n]	abs. EtOH-ether	188–191
XVIIB							
	—		—	3L	45[n]	abs. EtOH-ether	185–187
XVIII							
a	7209	N(*n*-amyl)$_2$	0.3	5R;3K	22[n]	1.5034–1.5037	183–185/0.5 mm.
b	8611	 $N(CH_3)(CH_2C_6H_5)$	0.1	6R;3L	10[n]	1.5664–1.5669	194–196/ 1 mm.

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{25}[e]	B.P. OR M.P., °C.[f]
XIX							
a	9515	N(*n*-octyl)$_2$	0.6	9SR;3K	5[n]	1.4967	238–240/2 mm.
b	8506	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	0.15	6Q;3L	23[n]	acetone	144–145
XXA							
a	6973	N(ethyl)$_2$.HCl	<0.15	5Q;3HK	55	EtOH-ether	148–149
b	7195	N(*n*-amyl)$_2$.HCl	<0.3	6Q;3L	23	EtOH-ether	95–96
c	7194	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	<0.06	6Q;3L	46[i]	EtOH-ether	196–197
d	7193	 $N(CH_2CH_3)(CH_2C_6H_5)\cdot HCl$	0.03	6Q;3L	30	EtOH-ether	146–147

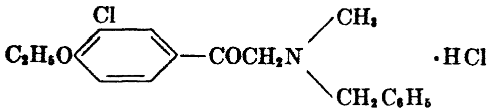
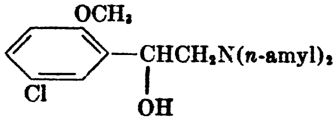
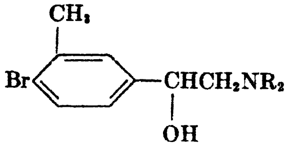
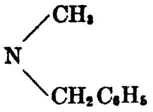
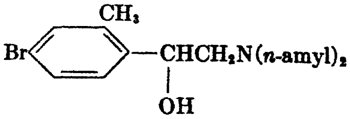
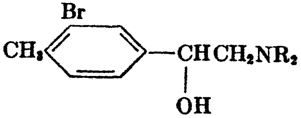
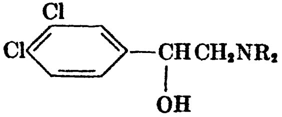
XXB							
	7975		<0.06	3L	51	EtOH-ether	193–194
XXI							
	—		—	5R;3JK	77	1.5050	180/1 mm.[u]
	8612	hydrochloride	0.15	Q	—	ether	165–167
XXII							
a	8416	N(*n*-butyl)$_2$	0.1	5R;3K	6[n]	1.5182–1.5188	174–176/2 mm.
b	6651	N(*n*-amyl)$_2$	0.1	5R;3K	12	1.5122^{27°	159–161/1.5 mm.
c	10012	N(*n*-octyl)$_2$	0.2	7SR;3M	20	1.5048	239–240/4 mm.
d	8948	 $N(CH_3)(CH_2C_6H_5)$	<0.1	7SR;3M	15	1.5807–1.5811	194–199/1-2 mm.

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR$_2$	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST FROM OR n_{D}^{20e}	B.P. OR M.P., °C.[f]
XXIII							
	8504		0.3	7SR;3M	6^n	1.5172–1.5176	185–191/1 mm.
XXIV							
a	8928	N(n-butyl)$_2$·HCl	<0.08	11RQ[k]	—	acetone-ether[t]	101–102
b	15440[q]	N(n-octyl)$_2$	0.06	11R[k]	53[k]	1.5090	262–272/2 mm.
b$_1$	—	b-hydrochloride	—	—[k]	—	—[k]	210–212[v,z,u]
XXVA							
a	9516	N(ethyl)$_2$·HCl	0.2	5RQ;3HK	57	EtOH-ether	123
a$_1$	—	a-picrate	—	—	—	ethanol	153

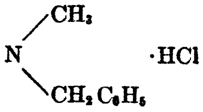
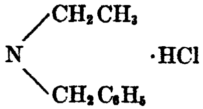
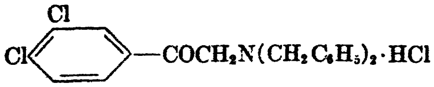
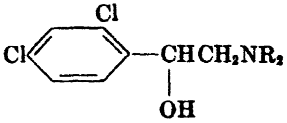
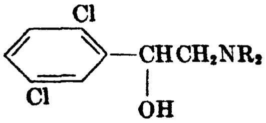
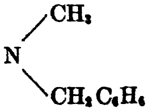
b	6550	N(*n*-butyl)$_2$	0.3	5S;3K	12	1.5189–1.5200	—^{g}
c	8417	N(*n*-amyl)$_2$	<0.6	5R;3K	34	1.5119	208–209/4 mm.
d	8505	N(*n*-octyl)$_2$	0.3 (1.5)^{b_2}	5R;3K	26	1.5061–1.5069$^{26°}$	244–248/2 mm.
e	7982	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	0.3	6RQ;3L	24	EtOH-*i*PrOH	195–196^e
f	8129	N(CH$_2$C$_6$H$_5$)$_2$·HCl	0.06	8Q;3N	63^i	CH$_3$OH	227–228
g	8503	 $N(CH_2CH_3)(CH_2C_6H_5)\cdot HCl$	0.15	5RQ;3K	54	isopropanol	134–136^e
h	12306	NH-*n*-octyl·HCl	<0.15	11T^k	56^r	acetone	227–229 dec.
i	—	N(cyclohexyl)$_2$·HCl	—	11Q^k	19^r	3:7-acetone-ligroin	204–205
XXVB							
	—		—	3L	—	abs. ethanol	215–216

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{25°}$ [e]	B.P. OR M.P. °C[f]
XXVI							
a	9003	N(*n*-butyl)$_2$·HCl	0.6	11RQ	40[r]	acetone-ether	97.5–98.5[e]
b	15377[g]	N(*n*-octyl)$_2$·HCl	0.5 (2)[b1]	11Q	47[k,r]	ether	110–113
XXVII							
a	11639	N(*n*-octyl)$_2$·HCl	0.6 (3)[b2]	11Q	47.5[r]	EtOH-ether	96–98
b	8971		<0.06	11R	35.5[r]	1.5772$^{25°}$	194–195/2 mm.

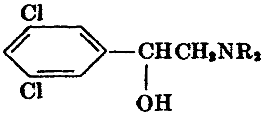
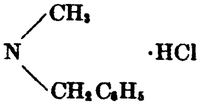
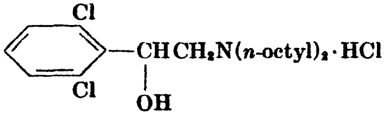
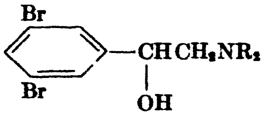
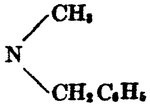
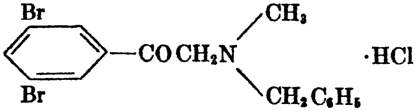
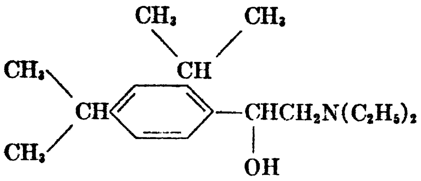
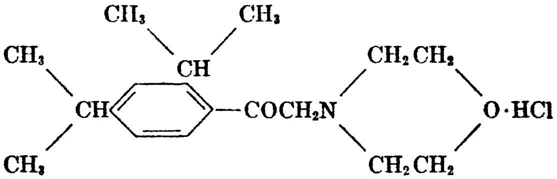
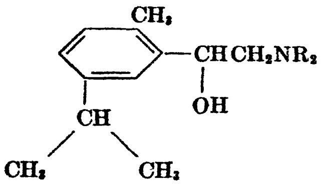
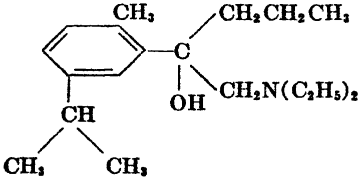
XXVIII							
a	8957	N(n-butyl)$_2$·HCl	0.1+	5RQ;3K	14	acetone-ether	127–128[e]
b	8972	 $N(CH_3)(CH_2C_6H_5)\cdot HCl$	0.3	5RQ;3K	60	acetone-ether	176–177
XXIX							
	8960		0.6	11Q	21[r]	abs. EtOH-ether	98–99.5
XXXA							
a	9037	N(ethyl)$_2$·HCl	0.2	6Q;3L	34[i]	abs. EtOH-ether	195–196
b	9902	N(n-amyl)$_2$·HCl	0.6	11SQ	32[r]	abs. EtOH-ether	127–128
c	9831	 $N(CH_3)(CH_2C_6H_5)$	0.1	6SR;3L	39	1.6020	200–202/2 mm.

TABLE I *con't.*

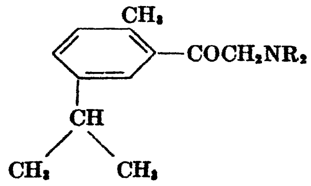
NO	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{20°}$	B.P. OR M.P., °C[f]
XXXB							
	—		—	3L	86	abs. EtOH	198–201
XXXIA							
	3635		<0.1	5TR;3K	24[n]	$1.5000^{24°}$	135–137/2 mm.
XXXIB							
	3551		<0.06	3L	70[n]	ethyl acetate	218–220 dec.

XXXIIA



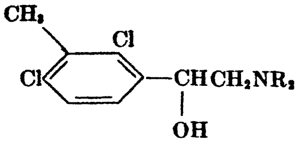
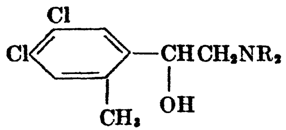
a	2598	N(ethyl)$_2$	<0.1	5R;3FK	32^n	—	131/4 mm.
b	2630	N(*n*-butyl)$_2$·HCl	<0.15	5RQ;3FK	13^n	acetone-ether	115–116
c	2597	piperidyl·HCl	<0.3	5Q^k	34^{i,n}	ethyl acetate	215.5–216
d	2599	morpholinyl·HCl	<0.06	5Q^k	21^{i,n}	ethyl acetate	178–179
e	6652		<0.06	—^{k}	9^n	1.5210$^{25°}$	153/5 mm.

XXXIIB

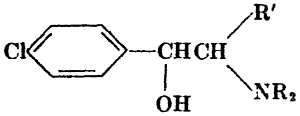


a	—	piperidyl·HCl	—	3FL	74^n	EtOAc-EtOH	191–192
b	2600	morpholinyl·HCl	<0.03	3FL	69^n	EtOAc-EtOH	208–209

TABLE I *cont'd*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{t°}$[e]	B.P. OR M.P., °C.[f]
XXXIII							
a	9832	$N(n\text{-butyl})_2$	0.2	7R;3M	60	$1.5175^{23°}$	186–188/1 mm.
b	10011	$N(n\text{-amyl})_2$	0.08	11R	40	$1.5257^{23°}$	204/1 mm.
c	12609	$N(n\text{-octyl})_2 \cdot HCl$	(4)[b2]	11RQ	29	ethyl acetate	116
d	10220	$N\begin{matrix}\diagup CH_3 \\ \diagdown CH_2C_6H_5\end{matrix} \cdot HCl$	0.04	11RQ	44	EtOH-ether	174
XXXIV							
a	11236	$N(n\text{-butyl})_2$	0.6	11R	60	$1.5311^{16°}$	191–193/0.5 mm.
b	11237	$N(n\text{-amyl})_2$	0.3	11R	51	$1.5266^{18°}$	202–203/0.5 mm.
c	11238	$N(n\text{-octyl})_2$	0.6 (2[b1], 4[b2])	11R	76	$1.5151^{18°}$	245/0.5 mm.
c_1	—	c-hydrochloride	—	Q	—	EtOAc-pet. ether	126–128

XXXVA



(a–d) R′ = $-CH_3$; (e, f) R′ = $-CH_2CH_3$; (g–j) R′ = $-CH_2CH_2CH_2CH_3$

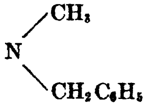
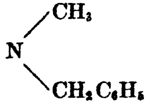
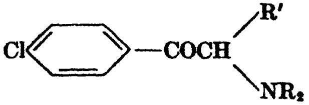
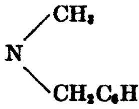
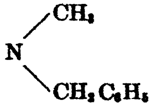
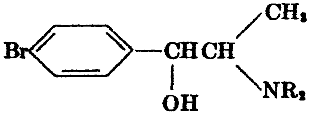
a	6750	N(*n*-amyl)$_2$	0.1	5TR;3K	25[n]	1.5001–1.5004	200–202/2 mm.
b	8400	N(*n*-octyl)$_2$	<0.03	5TR;3K	23[n]	1.4933–1.4936	206–210/1 mm.
c	6751	 $N(CH_3)(CH_2C_6H_5)$	<1.0	6U;3L	—[i]	EtOH	91–92
d	6654	piperidyl·HCl	<0.15	6Q;3L	—[i]	abs. EtOH-ether	198–200
e	6425	N(*n*-butyl)$_2$	<0.06	5TR;3K	20[n]	1.5040^{29°	136–139/1 mm.
f	6430	N(*n*-amyl)$_2$	<0.06	5TR;3K	30[n]	1.5001^{27°	163.5–165/1.5 mm.
g	6424	N(*n*-butyl)$_2$	<0.03	5TR;3K	17[n]	1.4998^{25°	155/1 mm.
h	7984	 $N(CH_3)(CH_2C_6H_5)$	<0.03	6R;3L	22[i,n]	1.5522–1.5525	181–184/1.5 mm.
i	—	piperidyl	—	6R;3GL	38[i,n]	1.5260^{26°	159/1 mm.
i_1	6655	i-hydrochloride	<0.06	Q	33[i,n]	abs. EtOH-ether	191.5–194.5[e]
j	10013	tetrahydroisoquinolyl·HCl	<0.03	6T;3G	—	acetone-ether	217–218 dec.[e]

TABLE I *cont'd*

NO.	SN^{a}	TYPE FORMULA —NR$_2$	Q^{b}	PREP. METHOD^{c}	YIELD (%)^{d}	CRYST. FROM OR $n_D^{20°}$	B.P. OR M.P., °C.^{f}
XXXVB			(a–b$_1$) R′ = —CH$_3$; (c–e) R′ = *n*-butyl.				
a	8310	 ·HCl	<0.06	3L	26^{n}	abs. EtOH-ether	196–197
b	—	piperidyl	—	3N	54^{n}	EtOH	64–65
b$_1$	6647	b-hydrochloride	<0.15	3P	47^{n}	abs. EtOH-ether	210–213
c	—	 ·HCl	—	3L	45^{n}	ethyl acetate	158–160.5
d	6646	piperidyl·HCl	<0.15	3GL	47^{n}	ethyl acetate	202–203 dec.
e	7400	tetrahydroisoquinolyl·HCl	<0.03	3G	76^{n}	butanone	202.5–206^{o}
XXXVI							
a	5045	N(*n*-butyl)$_2$	<0.1	5R;3K	—	1.5230	160–165/0.5 mm.^{x}
b	6657	N(*n*-amyl)$_2$	0.1+	5TR;3K	37	1.5095$^{27°}$	163.5/1.5 mm.

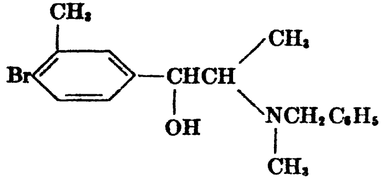
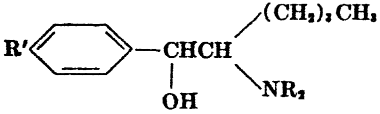
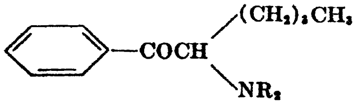
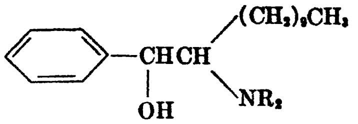
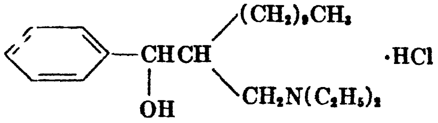
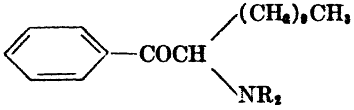
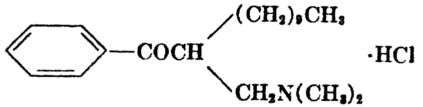
XXXVII							
	9586		<0.1	6U;3L	7^n	ethanol	103–104
XXXVIIIA			(a–c) R′ = —H; (d) R′ = —CH$_2$CH$_3$; (f) R′ = —C(CH$_3$)$_3$(e) R′ = —CH(CH$_3$)$_2$;				
a	3102	N(*n*-butyl)$_2$	<0.6	5R;3K	16^n	1.4918–1.4920	185–186/4 mm.
b	3096	piperidyl	<0.06	5R;3K	28^n	$1.5219^{25°}$	182/5 mm.
c	2740	morpholinyl·HCl	<0.15	5Q;3K	64^k	CH$_3$OH-ether	215–217
d	3251	N(*n*-butyl)$_2$	<0.03	5TR;3K	19^n	$1.4830–1.4836^{25°}$	140–150/1–2 mm.
e	3547	N(ethyl)$_2$	<0.06	5TR;3K	—	$1.4992^{22°}$	174–175/2 mm.^e
f	3297	N(ethyl)$_2$·HCl	<0.15	5RQ;3K	24^n	ethyl acetate	131–134
XXXVIIIB							
a	2742	piperidyl·HCl	0.06	3L	15^n	acetone	137–138
b	2741	morpholinyl·HCl	<0.06	3L	84^n	acetone	191–194

TABLE I *concluded*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n^{26}_D	B.P. OR M.P., °C.[f]
XXXIXA							
a	2013	N(ethyl)$_2$·HCl	<0.06	5Q;3K	46	acetone-ether	81–83
b	2612	piperidyl·HCl	<0.06	5Q;3K	—[k]	acetone	183–184
c	2625	morpholinyl·HCl	<0.06	5Q;3K	—[k]	acetone	178–180
XXXIXB							
	2748		<0.15	5Q[k]	8[n]	acetone	154–155
XXXIXC							
a	1628	piperidyl·HCl	<0.06	3L	67	acetone-ether	122–125
b	2626	morpholinyl·HCl	<0.02	3L	—	acetone	162–165

XXXIXD							
	—		—	—[k]	43[n]	acetone-ether	129–129.5

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[a] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned are tabulated in the Monograph (6).

[b] The symbol Q stands for quinine equivalent. The activities (6) listed in this table, except those in parentheses and otherwise specified by footnote, are against *P. gallinaceum* in the chick; most of them were determined at the National Institute of Health under the direction of Dr. G. Robert Coatney; a few were determined by Drs. L. T. Coggeshall and A. J. Porter at the University of Michigan (B-4), and by Drs. W. H. and L. G. Taliaferro and F. Coulston at the University of Chicago. [b1] These were the D-1 or G-5 tests against *P. lophurae* in the duck and were carried out at the Johns Hopkins Medical School under the direction of Dr. E. K. Marshall, Jr., and at the Squibb Institute for Medical Research under the direction of Dr. A. P. Richardson. [b2] Tests against *P. cathemerium* (G-4). [b3] These compounds were "slightly active" (*cf.* Ref. 6).

[c] This refers to the preparative method. The numbers and letters refer to the general "Procedures" and "Notes" given in the introduction.

[d] The yields are based on the α-bromo ketone unless otherwise specified. The yield is of good material though not usually fully purified.

[e] Refractive indices were taken at 20° unless otherwise specified in the body of the table.

[f] All melting and boiling points are corrected for exposed stem.

[g] Obtained as an oil which solidified on standing.

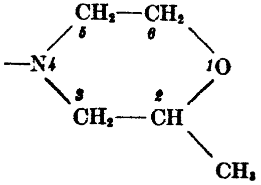
[h] As oil (b.p. 213–215°/2 mm.), n_D^{20} 1.5513.

[i] The yields based on the amino ketone hydrochlorides are: IAc = 33%; IIIB = 10%; IVa = 83%; b = 87%; c = 91%; g=91%; h = 87%; XVIAc=74%; XXAc = 90%; XXVAf = 80% (based on free base); XXXAa = 80%; XXXIIAc = 46%; d = 31%; XXXVAc = 52%; d = 52%; h =49%; i = 81%; i_1 = 70%.

[j] *i*PrOH = isopropanol.

[k] See experiment section for further details.

[m] 2-Methylmorpholinyl =



The yield is based on the parent acetophenone or the corresponding alkyl phenyl ketone.

Prepared in ice-cold absolute ether by passing in dimethylamine and standing overnight.

Drug Repository Number. These compounds were submitted for testing too late to be included in the Survey Monograph (6).

Yield based on the bromohydrin.

B.p. (of the free base): IIAp, 155°/2 mm.; s, 173–174°/1 mm.; u, 235–236°/4 mm.; XIa, 150–151°/2 mm.; c, 174–177°/2 mm.; XXVAe, 229–233°/1 mm.; g, 222–227°/1 mm.; XXVIa, 166–167°/1 mm.; XXVIIIa, 194–195°/3 mm.; XXXVIIIAe, 202–203°/15 mm.

Crystallized from an acetone-ether-petroleum ether mixture.

Not analyzed.

These melting points were determined *in vacuo*.

The sample decomposed on standing.

Hygroscopic.

Evaporated *in vacuo* at 206°.

constitute the chemical support for the results of the screening tests which have been published separately (6).

Two of the drugs described, namely, α-4-chlorophenyl-β-dioctylaminoethanol (IIAh) and α-4-chlorophenyl-β-N-tetrahydroisoquinolylethanol (IIAgg), were made by both of the above-outlined synthetic paths. The preparation of the former of these two compounds (IIAh) through the bromohydrin was considerably better than through the amino ketone (51% when calculated from the bromomethyl ketone). The expected and presumed mode of fission of the intermediate ethylene oxides involved[5] in the latter path through the bromohydrin was shown in both of the two cases to be as indicated above by the preparations also *via* the unequivocal path through the amino ketones, and by identification in each case of the two samples produced by the two different methods.

It is of interest to note that a successful practical short cut in the synthesis of the α-4-chlorophenyl-β-dioctylaminoethanol (IIAh) from the bromomethyl ketone was tried out in order to combine all of the steps into one operation, as follows: the *p*-chlorophenacyl bromide was added slowly to a refluxing solution of aluminum isopropoxide and excess dioctylamine and the reaction was completed in the usual way; upon working up the product the finished drug was isolated from the resulting mixture in 32% yield. This procedure was applied also in the case of α-(4-chloro-3-methylphenyl)-β-diamylaminoethanol (XVIAa) (yield 36%).

During the vacuum distillation of a number of ortho- and para-halogenophenyl amino alcohols of higher molecular weight (but not the meta-analogs) there were obtained crystalline by-products which were found in each case to consist of the hydrohalide of the secondary amine used in the preparation of the amino alcohol. This phenomenon was doubtless due to slow hydramine fission during the long heating involved, with production of the secondary amine and the halogenophenyl methyl ketone in which the nuclear halogen would be relatively more active than it was in the amino alcohol; this fission would be followed by interaction of the halogenophenyl methyl ketone with the secondary amine (or unchanged amino alcohol), with displacement of the now more active nuclear halogen, and with consequent formation and precipitation of a certain amount of the secondary amine hydrohalide. The significant activity of halogen ortho or para to an acetyl group has been reported under somewhat different but nevertheless analogous circumstances, for example, in the case of 2-bromo-4-methylacetophenone (11). To test this analogy and its bearing on the problem, dioctylamine and pure *p*-bromoacetophenone were heated together under conditions approximating those prevailing in the vacuum distillations of some of the amino alcohols, and the formation of significant amounts of dioctylamine hydrobromide was demonstrated.

This observed displacement of ortho and para halogen does not appear to be related to the reductive displacement which as been noted in the catalytic reduction of α-diethylamino-4-bromoacetophenone (12) to the amino alcohol. In the present cases, the aluminum isopropoxide used as the reducing agent would not be expected to have any such effect. Furthermore, in some instances the formation of the secondary amine hydrohalide was actually seen to occur *after* the reduction step and *during* the purification procedure involving the distillation of the free amino alcohols; also hydramine fission during distillation of certain other amino alcohols where no halide ion was produced, was observed in later experiments, notably in the case of α-(4-chlorophenyl)-β-ditridecylaminoethanol (IIAn) where the free secondary amine was isolated in small amounts and identified.

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[5] *Cf.* reference 10 and discussion, p. 1825.

EXPERIMENTAL

The following are generalized versions of the experimental methods employed in making the finished drugs.

The Preparation of the α-Bromomethyl Ketones

Procedure 1. The equivalent amount of bromine was added slowly under stirring and cooling to a commercial absolute ether solution of the methyl ketone. The bromination usually proceeded rapidly at 10–20°.

In *Procedure 2* the methyl ketone was brominated the same way except that a larger volume of solvent was used in order to ensure complete solution of the product, and the α-bromomethyl ketone was not isolated. The reaction solution was washed with water to remove hydrogen bromide and was dried; and aliquot portions were used directly in the reaction with the amines.

The Preparation of the Amino Ketones[8]

Procedure 3. An ethereal solution of the α-bromomethyl ketone (which, in some cases had not been isolated and purified) was treated under stirring with the secondary amine[7] (2–2.5 equivalents unless otherwise specified). The mixture was allowed to stand for eight to forty-eight hours, or until no further precipitation of the secondary amine hydrobromide could be observed. The secondary amine hydrobromide was removed by filtration and the amount thus obtained served to indicate the extent to which the reaction had gone.

Procedure 4. In a few instances the amino ketone was obtained by reacting the α-bromomethyl ketone in ether with one equivalent of the dialkylamine in the presence of an excess of dilute sodium or potassium carbonate. The resulting heterogeneous mixture was shaken for twelve to forty-eight hours; the ether layer was separated, washed with water and dried over sodium sulfate.

Preparation of the Amino Alcohols by Aluminum Isopropoxide Reduction of the Amino Ketones

Procedure 5. The crude free base was dissolved in dry isopropanol, mixed with 3–6 equivalents of 3 *N* aluminum isopropoxide and the mixture was heated under partial reflux at such a rate as to permit the slow distillation of acetone from the top of either a modified Hahn[8] or helices-packed column for 1–48 hours (until significant amounts of acetone could no longer be detected in the distillate by means of 2,4-dinitrophenylhydrazine test solution). Isopropanol was removed under reduced pressure (warming) and the residue was digested with excess 6–10 *N* sodium hydroxide. The mixture was then diluted with water and extracted with ether, and the ether solution was washed with water and then with saturated salt solution and was dried over sodium sulfate.

Procedure 6 (reduction of the purified amino ketone hydrochloride which had been prepared according to Note L), *Procedure 7* (reduction of the crude oily amino ketone hydrochloride prepared according to Note M), and *Procedure 8* (reduction of the pure free base prepared according to Note N), were carried out like Procedure 5.

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[8] *Cf.* Ref. 8, p. 196.

Procedure 9. The use of anhydrous aluminum chloride in reduction. In several instances one-half to one mole of anhydrous aluminum chloride per mole of the amino ketone (free base) was added to the aluminum isopropoxide solution in order to supply halide ion in concentration comparable to or greater than that involved when the salts of the amino ketones were used. The actual reduction was carried out as in Procedure 5. In one case, namely, XIXa, comparative preparations were carried out on the free base, with and without added aluminum chloride; the use of the aluminum chloride greatly improved the yield.

Preparation of Amino Alcohols Through the α-(Bromomethyl)benzyl Alcohols

Procedure 10. The aluminum isopropoxide reduction of certain of the α-bromomethyl ketones (3, 8, 9, 10) was carried out according to Procedure 5 until acetone could no longer be detected in the distillate (the reaction time varied from four to forty-eight hours). The isopropanol was evaporated under reduced pressure and the residue was shaken with cold 6 *N* sulfuric acid.

Procedure 11. The condensation of the bromohydrins with amines was carried out by dissolving the bromohydrin and two equivalents of the secondary amine in xylene or toluene and heating under reflux. In each case, after the reaction appeared to be complete, the mixture was cooled and diluted with absolute ether, and the precipitated hydrobromide of the secondary amine was filtered. The filtrate was washed, first with alkali, then with water, and was dried over sodium sulfate. The solvent was removed by distillation and the residue was purified by one or more of the methods listed in the Notes Q–W.

Notes to Procedures 1 and 2. (A) If the α-bromomethyl ketone precipitated from the cooled reaction mixture, the product (almost colorless) was filtered, washed with water, air-dried, and if necessary recrystallized from a suitable solvent (usually ethanol).

If the product did not precipitate, the reaction solution was washed with water and with dilute sodium carbonate, dried over sodium sulfate and concentrated. The crude product was then obtained either (B) as an oil in which case it was purified by vacuum distillation, or (C) as a solid in which case it was usually recrystallized, or in a few cases (D) vacuum distilled and then when possible (E) recrystallized.

Notes to Procedures 3 and 4. When more than the theoretical amount of the amine was used in the reaction (two equivalents in Procedure 3 and one in Procedure 4) the excess was occasionally removed as follows:

(F) In the case of water-soluble amines the excess amine was removed by extraction with water or saturated sodium chloride solution, and the ether solution was dried over sodium sulfate.

(G) In several cases, after extraction of the amine with water, the amino ketone was extracted with dilute hydrochloric acid and reprecipitated with sodium hydroxide and again extracted into ether.

(H) When the excess of the amine was not removed by extraction, it was removed by evaporation under reduced pressure.

(J) In the case of water-insoluble amines usually only the calculated two equivalents of amine was used and any excess remaining was not removed until after the amino ketone had been reduced to the amino alcohol.

Finally in all cases, the ethereal solution of the amino ketone was evaporated under reduced pressure. The residue consisted of a yellow or brown oil or a crystalline solid. The oily amino ketones were treated in one of the following ways:

(K) Reduction directly to the amino alcohol (Procedure 5).

(L) Solution in a suitable solvent, usually ether, and conversion into a crystalline hydrochloride by acidifying the solution with ethereal hydrogen chloride. The resulting mixture was diluted with ether and the product was filtered, washed with ether, and dried.

This product was often pure enough for use in the next step, or was further purified by recrystallization before reduction.

(M) Solution in a suitable solvent and conversion to an *oily* hydrochloride as in (L). The solvent was decanted; the residual oil was washed with ether by decantation, and without further purification was reduced to the amino alcohol.

The crystalline amino ketone (free base) was purified by (N) recrystallization or (P) conversion to and recrystallization of the hydrochloride.

Notes to Procedures 5–9. The partial decomposition of the higher-boiling amino alcohols during distillation was doubtless responsible for the low yields obtained in many cases in this investigation. Satisfactory results were usually obtained whenever such experiments were repeated under more favorable conditions for the distillation, involving such factors as better vacua, exclusion of oxygen by the use of an atmosphere of nitrogen, heating of the fractionating column, and in some cases resort to evaporation under low pressures onto a cold-finger drip-condenser under conditions approximating those in a molecular distillation.

(Q) The amino alcohol was precipitated from the ether solution as the hydrochloride by the addition of ethereal hydrogen chloride; it was then purified by crystallization, usually by dissolving in absolute ethanol and adding anhydrous ether.

If the crude free base did not readily form a crystalline hydrochloride it was (R) fractionally distilled under reduced pressure or (S) molecularly distilled and then fractionally distilled under reduced pressure and ordinary conditions. In the case of several of the amino alcohols of high molecular weight it was necessary to use a combination of (R) and (S) to effect purification.

(T) In several cases the ether extract containing the crude amino alcohol was extracted with 1–2 *N* hydrochloric acid to remove the basic material. Except for the few cases where the salt separated at this point, the acid layer was then neutralized with sodium hydroxide solution and the free base was extracted into ether. The amino alcohol was isolated according to one of the above methods.

In a few cases the amino alcohol separated as a solid after digestion of the residue with sodium hydroxide solution, and was filtered, washed with water and purified by (U) crystallization or (W) conversion into the hydrochloride followed by crystallization.

Notes to Procedure 10. (Y) In most instances the product separated as a solid and could be purified by crystallization from ligroin or 80% ethanol. (Z) In other instances the product was extracted into ether; the ether extract was washed with water, dried over sodium sulfate or potassium carbonate, and evaporated under reduced pressure; and the residue was fractionated under reduced pressure.

I. THE α-PHENYL-β-DIALKYLAMINOETHANOLS

These amino alcohols were prepared by condensation of phenacyl bromide with the appropriate secondary amine followed by aluminum isopropoxide reduction of the amino ketone to the amino alcohol. The few compounds of this type reported in the literature include the dimethyl (14, 15) and dibutylamino (16) compounds; the latter was made by the above method and reported since the present work was completed.

EXPERIMENTAL[6]

The preparation of α-dibenzylaminoacetophenone (IB) was carried out by the method of Busch and Hefele (13), in slightly improved yield (71%); m.p. 80–82° (B. and H., 81°); it decomposed on long standing.

α-Phenyl-β-dibenzylaminoethanol hydrochloride (IAf) (See Procedure 8UW.) A mix-

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[6] All melting points and boiling points given in this paper are "corrected".

ture of 16 g. of α-dibenzylaminoacetophenone and 200 ml. of 1.5 *N* aluminum isopropoxide was heated under reflux for four hours, when the distillate gave a negative test for acetone. The isopropanol was evaporated under reduced pressure, and the residue was hydrolyzed by adding 5 ml. of water and then 50 ml. of 50% sodium hydroxide. After shaking the resulting mixture for two hours the oil which separated was extracted into 300 ml. of ether, washed with water, recovered by evaporation of the solvent under reduced pressure, and dissolved in ethanol. As the ethanol slowly evaporated, the amino alcohol (free base) crystallized; m.p. 52–53°; it was converted to the hydrochloride from dry ether by acidifying with ethereal hydrogen chloride; 14.5 g. (65%, calculated from phenacyl bromide); m.p. 211°. One recrystallization from 1:1 absolute ethanol-isopropanol gave 12.5 g. melting at 213°.

II. THE α-4-CHLOROPHENYL-β-DIALKYLAMINOETHANOLS

With one exception, namely, α-4-chlorophenyl-β-N-(2-hexylpiperidyl)ethanol (IIA11), the amino alcohols reported in this section were prepared through the amino ketones by reduction with aluminum isopropoxide. Failure was experienced in those condensations with α-bromomethyl ketones which involved the use of amines carrying a branch chain in the α-position, namely, 2-hexylpiperidine, diisopropylamine, and dicyclohexylamine. This phenomenon was observed also in other series, for example, the 3,4-dichloro. The amine in each case appeared to have reacted with the bromomethyl ketone, as indicated by the amount of secondary amine hydrobromide obtained, but no amino alcohol was obtained on working up the reduction mixture. The reaction probably did not involve reductive fission of the amino ketone during the aluminum isopropoxide reduction. In fact it seems more likely that the amino ketone had not been formed at all, or only in very small amounts, as was shown in one case, namely, the reaction of dicyclohexylamine with *p*-chlorophenacyl bromide in ether; this reaction produced a quantitative yield of the secondary amine hydrobromide after seventy-five hours at room temperature, and addition of ethereal hydrogen chloride precipitated the rest of the unused secondary amine, together with 2 g. of a yellow nitrogen-free crystalline substance (m.p. 188–190°) which has not yet been identified. This failure of the branched-chained amines to react with the bromomethyl ketone may be due to steric factors; the basic character of the amine evidently promotes enolization and condensation.

It appeared that generally better yields of the amino alcohols were obtained when the hydrochlorides rather than the free bases were used in the reduction (*cf.* 12), although only one control experiment was carried out to show this. Also it appeared that the yields depended to a large extent on the purity of the materials used.

The hydrochlorides of the higher dialkylamino compounds from dioctylamino up are progressively more soluble in ether than in water and may be recrystallized from ether.

The alkylamino alcohols of low molecular weight could be distilled under reduced pressure. The diundecyl, didodecyl, and ditridecylamino alcohols, however, could not be vacuum distilled without decomposition and hydramine fission. No indication of displacement of the para-chlorine was observed in these particular cases, however. Several low-pressure vacuum evaporations onto a cold-finger condenser were necessary to effect a purification and to minimize hydramine fission. In the case of the ditridecylamino compound, distillation of a pure sample which had been obtained by several previous vacuum evaporations gave a distillate containing large amounts of a solid which was isolated and identified as the secondary amine (base) by conversion into its hydrochloride.

A few of the amino alcohols in this series, namely, dioctyl and tetrahydroisoquinolyl, were made both through the amino ketones and through the bromohydrin, and, as mentioned above, the β-N-(2-hexylpiperidyl) compound (IIA11) could be made only through the bromohydrin.

In this series two amino ketones were made by the Mannich reaction on *p*-chloroacetophenone, namely, the di-*n*-amyl and benzylmethylamino compounds. Reduction of these as the hydrochlorides by aluminum isopropoxide gave very poor results due to reductive fission of the dialkylamino groups. In the case of the benzylmethylamino compound, the secondary amine produced by reductive fission was actually isolated in 57% yield and identified. Because of this effect no amino alcohols of the type desired were obtained in this series in sufficient quantity for screening tests.

EXPERIMENTAL[6]

α-Bromo-4-chloroacetophenone, prepared by Collet (17) by bromination in carbon disulfide or glacial acetic acid solution, was made in ether according to Procedure 1A in yields of 85%.

α-Bromomethyl-4-chlorobenzyl alcohol was prepared according to Procedure 10Z. A solution of 23.5 g. (0.1 mole) of α-bromo-4-chloroacetophenone in 350 ml. of 1.3 *N* aluminum isopropoxide was refluxed for thirty-two hours. During the reduction, the acetone was collected and the amount determined by titration (*cf.* 18); 75%. The isopropanol was removed under reduced pressure and the residue hydrolyzed with dilute sulfuric acid. The bromohydrin was extracted into ether, washed with dilute sulfuric acid, sodium chloride solution and water, and dried over sodium sulfate. In one experiment the ether was evaporated, and the residual oil vacuum distilled and crystallized from ligroin; in another experiment the crude product was crystallized directly from ligroin, 15 g. (64%), m.p. 61–62°.

Anal. Calc'd for $C_8H_8BrClNO$: C, 40.80; H, 3.42.
Found: C, 40.74; H, 3.99.

α-4-Chlorophenyl-β-di-n-octylaminoethanol (*IIAh*). (a) Preparation from the bromomethyl ketone according to Procedures 3K;5R resulted in a yield of 38% of the amino alcohol (calculated from the bromomethyl ketone). The hydrochloride prepared from ether may be crystallized from dioxane or acetone, or preferably from ethanol by adding water until the solution becomes turbid, adding seed crystals, and allowing the mixture to cool in the ice-bath for several hours. It melted at 86–87°.

(b) In the hope of discovering a satisfactory short cut to the above method of preparing this amino alcohol, the following experiment was performed. A hot isopropanol solution of one equivalent of α-bromo-4-chloroacetophenone was added over a period of forty-five minutes to a refluxing isopropanol solution of 1.5 molal equivalents of aluminum isopropoxide and 1.5 equivalents of dioctylamine.[7a, c] The reduction to, and isolation of, the amino alcohol was carried out in accordance with Procedure 5R; yield, 32%.

[7(a)] Quantities of certain of the primary and secondary amines used in this research were prepared or secured by the Columbia University group under the direction of Dr. R. C.

(c) The amino alcohol was also prepared from the bromohydrin according to Procedure 11R (0.034 mole of the bromohydrin and 0.0704 mole of dioctylamine in 30 ml. of xylene, refluxed for 17.5 hours); it distilled at 215–217° (2 mm.); yield, 10.7 g. (80% calculated from the bromohydrin, or 52% calculated from the bromomethyl ketone).

α-4-Chlorophenyl-β-N-tetrahydroisoquinolylethanol (*IIAgg*). The hydrochloride precipitated upon attempted extraction of the ether solution with hydrochloric acid; 10.5 g. (59%), m.p. 204–209°. After crystallization from 100 ml. of water it melted at 229–231° (vac.).

The mother liquor from the crystallization was made basic and the remaining free amino alcohol was extracted with ether and crystallized from petroleum ether; white plates; m.p. 90–91°.

This amino alcohol was prepared also according to Procedure 11Q. A solution of 2 g. of the bromohydrin and 4.5 g. (0.034 mole) of tetrahydroisoquinoline in 15 ml. of xylene was refluxed for thirteen hours. The mixture was diluted with ether and the precipitate of amine hydrobromide was filtered. Ethereal hydrogen chloride precipitated the hydrochloride, which was crystallized from 30 ml. of water; 1.82 g. (66%); m.p. 197–217°. The free base isolated from the filtrate melted at 91° after two crystallizations from petroleum ether. A mixture melting point with the base prepared by reduction of the amino ketone showed no depression.

α-4-Chlorophenyl-β-di-n-dodecylaminoethanol (*IIAm*) was purified by a series of fractional vacuum evaporations of material which had previously distilled at 239–262° (2 mm.), onto a cold-finger condenser at 144–162° (2 mm.).

α-4-Chlorophenyl-β-di-n-tridecylaminoethanol (*IIAn*) distilling at 231–281° (2 mm.) was freed from ditridecylamine[7a], by dissolving in ethyl acetate and adding ethereal hydrogen chloride to precipitate the secondary amine hydrochloride. Fractions were combined from several vacuum evaporations and distillations, and material so obtained was then fractionally evaporated at 2 mm. The fraction evaporating over a temperature range up to 150° contained large amounts of ditridecylamine which was isolated and identified. The fraction evaporating at 152–173° was analyzed.

β-Di-n-amylamino-4-chloropropiophenone hydrochloride (*IICa*). A mixture of 31 g. of 4-chloroacetophenone, 23 g. of diamylamine hydrobromide, 18 g. of paraformaldehyde, 75 ml. of absolute ethanol, and 2 ml. of ethanolic hydrogen chloride was refluxed for twenty-four hours and the solvent evaporated in a current of air. The residual oil was treated with dilute sodium hydroxide and extracted with ether, washed, dried, and recovered by evaporation of the solvent. It was converted into the hydrochloride by dissolving in acetone and acidifying (Congo Red) with ethereal hydrogen chloride; 24 g. (67%); m.p. 65–72°. Six crystallizations from acetone by adding dry ether gave a product of m.p. 100–103°.

Reduction by aluminum isopropoxide (Procedure 6) gave a product of low and wide boiling range which evidently contained a large amount of diamylamine formed through reductive fission.

β-Benzylmethylamino-4-chloropropiophenone hydrochloride (*IICb*); made like IICa in 63% yield (17 hours refluxing); recrystallized from ethanol; m.p. 170–172°.

In the aluminum isopropoxide reduction (Procedure 6) of IICb (refluxing for 9 hours) a crystalline salt was obtained in 57% yield from ether by ethereal hydrogen chloride; it was identified as benzylmethylamine hydrochloride.

III. THE α-4-BROMOPHENYL-β-DIALKYLAMINOETHANOLS

Seventeen new amino alcohols in this series were prepared through the reaction between the α-bromomethyl ketone and the appropriate amine followed by

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Elderfield. (b) Some of the amines were made under the direction of Dr. W. S. Cottle, at Rutgers University. (c) Several were supplied by the Sharples Co. (d) A number of the benzylalkylamines are new and are described in a separate paper (Ref. 90).

aluminum isopropoxide reduction of the amino ketone. Ten amino ketones were also isolated in this series, one of which, α-N-morpholino-4-bromoacetophenone, has been prepared previously (19). The preparation of lower members of this series was omitted because during the course of this investigation it was learned that they were being made in another laboratory (12).

The attempt to obtain homologs of typical amino alcohols led to the study of the Mannich reaction in this series. As in the case of the *p*-chloro analogs, the β-amino ketones could be obtained readily but reduction did not appear to be practical in the few preliminary trials. In one case, that of the dipropylamino compound (IIIB), reduction gave a small yield (10%) of the desired γ-amino alcohol.

EXPERIMENTAL[6]

α,4-Dibromoacetophenone (17, 20, 21) was prepared in the usual way in yields of 90% (Procedure 1A).

α-4-Bromophenyl-β-di-n-amylaminoethanol (*IIIAb*) (illustrating Procedures 5TR;4K). To a 200-ml. dry ether solution of 27.8 g. (0.1 mole) of α,4-dibromoacetophenone, cooled in an ice-bath, was added 17 g. (0.108 mole) of diamylamine. After the initial reaction had subsided, 140 ml. of 15% sodium carbonate was added, and the resulting mixture was shaken mechanically for two days. The ethereal solution was washed and dried over sodium sulfate; the solvent was evaporated under reduced pressure, and the residual oil was dissolved in dry isopropanol and 100 ml. of 3 *N* aluminum isopropoxide. The reduction required one day (refluxing). The isopropanol was evaporated under reduced pressure, and the dark residue was digested with 8 *N* sodium hydroxide. The reduction products were extracted into ether, and the ether layer was shaken with 6 *N* hydrochloric acid. Three layers formed. The ether layer containing the non-basic matter was discarded. The aqueous and oily layers were neutralized with 5 *N* sodium hydroxide solution, and the amino alcohol was extracted into ether; the ether layer was washed and dried over sodium sulfate with simultaneous Darco treatment. The product was isolated and distilled under reduced pressure; 33.1 g; b.p. 167–170° (2 mm.). A second treatment in ether solution with Darco and redistillation under reduced pressure gave 18.6 g. (52%).

α-4-Bromophenyl-β-di-n-octylaminoethanol (*IIIAf*) (illustrating Procedures 5TR,3K, and the loss of nuclear halogen). To a suspension of 27.8 g. (0.1 mole) of the α-bromomethyl ketone in 100 ml. of dry ether, was added under cooling and stirring 49 g. (0.2 mole) of dioctylamine. After the reaction mixture was allowed to stand at room temperature for eight hours, 24 g. (94%) of the secondary amine hydrobromide precipitated. The reduction was carried out as described above (for IIIAb). Fractionation under reduced pressure gave 6 g. (14%) of slightly yellow product.

One of the fractions contained large amounts of a solid mixed with the oily product. This fraction was diluted with dry ether and the mixture was filtered. Recrystallization of the solid from ethanol-ligroin gave a colorless product which was identified as dioctylamine hydrobromide by analysis (Calc'd for $C_{16}H_{35}N \cdot HBr$: N, 4.35. Found: N, 4.52), and by melting point and mixture melting point.

α-[4-(2-Ethylmorpholinyl)]-4-bromoacetophenone hydrochloride (*IIICf*) (illustrating Procedure 3GL). Thirty-two grams (0.28 mole) of 2-ethylmorpholine[7b] was added slowly with stirring to a suspension of 35 g. (0.13 mole) of the α-bromomethyl ketone in 350 ml. of dry ether. Filtration after three hours gave 24.4 g. (99%) of the secondary amine hydrobromide. The ether filtrate was extracted four times with 200-ml. portions of water, and then three times with 175-ml. portions of 1 *N* hydrochloric acid. The acid solutions were combined and neutralized with 5 *N* sodium hydroxide. The oil which separated was extracted into 250 ml. of ether; the ether layer was separated, and the solvent was evaporated under reduced pressure. After the residual oil had been dried further under a good vacuum, it was dissolved in 300 ml. of absolute ether and neutralized (Congo Red) with ethereal hydrogen chloride. The ether was decanted from the amino ketone hydrochloride which precipitated. This crude product was digested with acetone; 37 g. (82%); m.p. 220–222° dec. Recrystallization from ethanol gave 26 g. of pure product melting at 228° dec. *in vacuo.*

α-4-Bromophenyl-β-[4-(2-ethylmorpholinyl)]ethanol hydrochloride (IIIA1) (illustrating Procedure 6TQ). Thirty grams of a suspension of 30 g. of the amino ketone hydrochloride in 250 ml. of 1.8 *N* aluminum isopropoxide was heated under reflux for 3.5 hours, when no more acetone was being produced. The isopropanol was distilled under reduced pressure. To the residue was added 5 ml. of water and then 70 ml. of 10 *N* sodium hydroxide. After one hour of shaking, the oil which separated was extracted into 300 ml. of ether; the ether layer was separated, washed well with water, and extracted twice with 200-ml. portions of 1 *N* hydrochloric acid. The combined acid solution was made alkaline (litmus) with 5 *N* sodium hydroxide, and the oil which separated was extracted by ether. The ether layer was separated, washed with water, dried over sodium sulfate, and neutralized with ethereal hydrogen chloride. The precipitated amino alcohol hydrochloride was recrystallized from a 9:1 isopropanol-methanol mixture; 19 g. (63%); m.p. 186–187°.

The reaction between 4-bromoacetophenone and di-n-octylamine. A mixture of 4 g. (0.02 mole) of the bromomethyl ketone and 9.6 g. (0.04 mole) of dioctylamine was heated at 235—245° for thirty minutes, conditions simulating those involved in the vacuum distillation of the amino alcohols. After the mixture had cooled, dry ether was added, and 0.5 g. of dioctylamine hydrobromide precipitated and was identified.

β-Di-n-propylamino-4-bromopiopuophenone hydrochloride (*IIIDa*) was made by refluxing for twenty-one hours a mixture of dipropylamine hydrochloride, *p*-bromoacetophenone, paraformaldehyde, and a small amount of concentrated hydrochloric acid with dioxane or absolute ethanol as solvent. The product was obtained as an oil and was separated from unreacted dipropylamine by fractional precipitation of the hydrochlorides with standard ethereal hydrogen chloride.

α-4-Bromophenyl-γ-di-n-propylaminopropanol hydrochloride (*IIIB*). One gram of IIIDa was added to 12 ml. of warm 2 *N* aluminum isopropoxide. After refluxing for twenty minutes and working up the product, and crystallizing it as the hydrochloride, 0.1 g. of pure material was obtained.

The *di-n-butylamino* compound (IIIDb) was made like IIIDa using absolute ethanol as solvent.

IV. THE 4-IODOPHENYL-α-DIALKYLAMINO KETONES AND ALCOHOLS

Seven amino alcohols and three amino ketones were made from 4-iodoacetophenone. Attempts to make the diisopropylamino compounds failed, evidently due to steric factors which interfered with the formation of the amino ketone.

EXPERIMENTAL

4-Iodoacetophenone. The preparation by the Friedel-Crafts reaction in carbon disulfide (22), reported as proceeding in 80–95% yields using acetyl chloride and resublimed anhydrous aluminum chloride, gave only poor yields in our hands using technical aluminum chloride. Large amounts of iodine were liberated during the reaction. This may have been caused by impurities in the aluminum chloride, for example, iron (*cf.* Ref. 23). The yields were brought to 76% by adding the iodobenzene slowly to the refluxing reaction mixture.

This product was brominated according to Kimura (22).

V. THE α-4-FLUOROPHENYL-β-DIALKYLAMINOETHANOLS

EXPERIMENTAL[6]

4-Fluoroacetophenone (24, *cf.* also Ref. 25) was prepared by slow dropwise addition of 100 g. of acetic anhydride into a well-stirred mixture of 112 g. of fluorobenzene, 465 g. of anhydrous aluminum chloride and 700 ml. of carbon disulfide, with subsequent refluxing for two hours; yield 100 g. (62%); b.p. 195°.

α-Bromo-4-fluoroacetophenone was prepared by dropwise addition of 61 g. of bromine into a stirred solution of 43 g. of 4-fluoroacetophenone in 200 ml. of absolute ether. After washing the solution and distilling, a fraction boiling between 140–150° (5 mm.) was collected (the bulk distilled at 148°); yield 70 g. (96%); it crystallized on standing; m.p. 48–49°.

Anal. Calc'd for C_8H_6BrFO: C, 44.27; H, 2.79.
Found: C, 44.52; H, 3.00.

α-4-Fluorophenyl-β-di-n-octylaminoethanol (*Va*). A mixture of 38 g. of dioctylamine, 21 g. of α-bromo-4-fluoroacetophenone, 125 ml. of ether, 25 g. of potassium carbonate, and 10 ml. of water was shaken for twenty-four hours; the ether solution was separated and evaporated, and the residual oil (46 g.) was added to 150 ml. of 3 *N* aluminum isopropoxide. After refluxing for two hours the solvent was evaporated on a water-bath at 50°. Hydrolysis with 3 *N* hydrochloric acid, treatment of the precipitated hydrochloride (an oil) with 10% sodium hydroxide and extraction with ether, gave the free base as an oil which distilled at 195–197° (1 mm.) (the major portion distilled at 196°); yield 26 g. (56%).

α-4-Fluorophenyl-β-(benzyl-n-butylamino)ethanol (*Vc*). The amino ketone (Procedure 3) formed quickly upon interaction of 21 g. of the α-bromo ketone and 52 g. of benzylbutylamine[7d] in 125 ml. of absolute ether (15 min.); crude yield 33 g. This product was reduced (Procedure 5) and the reaction complex was hydrolyzed with 50% potassium hydroxide. The oily product was dissolved in ether and treated with 6 *N* hydrochloric acid; the hydrochloride separated as a third layer, and was isolated and converted under ether to the base with 10% sodium hydroxide. The resulting oil distilled at 172–174° (1 mm.) and was redistilled; the major portion boiled at 173.5° (1 mm.); yield 22 g. (66%).

VI. THE α-3-CHLOROPHENYL-β-DIALKYLAMINOETHANOLS

3-Chloroacetophenone, first made by the decarboxylation of α-carbomethoxy-3-chloroacetophenone (26), has been obtained in quantity through *meta*-nitration of acetophenone (27), followed by reduction, diazotization and the Sandmeyer reaction. It had been observed (27) that the use of nitric acid alone in the nitration of acetophenone gives a mixture of isomeric acetophenones, whereas the nitric and sulfuric acid mixture gives chiefly the meta compound. It has usually been necessary to limit the size of the run because either an undue temperature rise, or the very slow addition of the nitrating mixture necessary to prevent the rise, has an adverse effect on the purity of the product (28). Addition of dry-ice directly to the reaction mixture is advantageous in the nitration of a substituted acetophenone (29), and dry-ice has been used more recently in the nitration of acetophenone itself (30, 12). It was found here that at temperatures below −30° the viscosity became too great for effective stirring. Excellent results were obtained at reaction temperatures of −20° to −15° in batches of six times the size formerly considered as the optimum (30).

EXPERIMENTAL

Preparation of 3-nitroacetophenone (*cf.* ref. 12, 29, 30). A 3-liter 3-necked flask charged with 900 ml. of concentrated sulfuric acid and equipped with a stainless steel stirrer was mounted in an insulated 10-quart pail filled with ethanol to which dry-ice was added as needed (about 10 lbs. was required). Acetophenone (360 g., 3 moles) was added slowly, followed by the nitrating mixture consisting of 360 ml. of concentrated sulfuric acid and 240 ml. (3.9 moles) of nitric acid (precooled to 0°). The additions were made at such a rate that the heat evolved prevented the mixture from cooling to the point of freezing or becoming too viscous to stir; the actual mixture temperature ranged from −30° to −20° at the beginning of the nitration, and from −20° to −15° as the last of the nitrating mixture was added. The actual time required for adding the nitrating mixture was about forty-five minutes, and a few minutes later the mixture became extremely viscous; the cooling bath was then removed, and when the mixture had warmed sufficiently to flow, it was poured with stirring into 13.5 l. of ice and water. The cream-colored precipitate was washed repeatedly with water and once with ice-cold ethanol; it was pure enough for further use; yield 198 g. (81%).

Preparation of 3-chloroacetophenone. The directions used were practically identical with those in "Organic Syntheses" (31) for the preparation of 3-chlorobenzaldehyde; the yield was 68%. It was *brominated* according to Procedure 1, using carbon tetrachloride as a solvent.

VII. THE α-2-CHLOROPHENYL-β-DIALKYLAMINOETHANOLS

EXPERIMENTAL[6]

α-Bromo-2-chloroacetophenone. An ether solution of 87.5 g. (0.5 mole) of *o*-chlorobenzoyl chloride (32) was added dropwise with stirring to a cold solution of 1.5 moles of diazomethane in 2.5 l. of ether, and the mixture was allowed to stand overnight. Treatment with 215 ml. of 40% hydrobromic acid in an equal volume of ether (effervescence), washing the ether layer with water and sodium bicarbonate solution, drying over sodium sulfate and distilling off the ether, gave an oil which was vacuum distilled [92 g. (79%); b.p. 129–131° (4.5 mm.)] and redistilled; b.p. 97.5–98° (1 mm.); n_D^{20} 1.5903.

Anal. Calc'd for C_8H_6BrClO: C, 41.15; H, 2.59.
Found: C, 41.33; H, 2.75.

VIII. THE α-3-BROMOPHENYL-β-DIALKYLAMINOETHANOLS

The route for the preparation of 3-bromoacetophenone, needed for this series, was the reduction of 3-nitroacetophenone (see section VI), followed by diazotization and treatment with cuprous bromide.

EXPERIMENTAL[6]

Preparation of 3-bromoacetophenone followed approximately the old procedure (33) starting with 3-nitroacetophenone, reducing this with stannous bromide (*cf.* 34), diazotizing the 3-aminoacetophenone in dilute hydrobromic acid and treatment with cuprous bromide. Light yellow oil, *b.p.* 102–106° (4 mm.); yield 63%.

Bromination was carried out according to Procedure 1DE; b.p. 154–159° (10 mm.); m.p. 48°; recrystallized from ligroin, m.p. 51° (E., G., and J., 51°).

IX. α-2-BROMOPHENYL-β-BENZYLMETHYLAMINOETHANOL

2-Bromoacetophenone, the starting material, [first prepared through nitration of acetophenone, separation of the ortho and meta nitro derivatives, reduction and diazotization (35, 36)] has been made more conveniently from 2-bromobenzoic acid through the acid chloride, the amide, and the nitrile [by addition of methylmagnesium iodide (37) to the latter]. An effort was made to obtain 2-bromoacetophenone directly by methylation of the 2-bromobenzoyl chloride with dimethylcadmium, following the successful work of Gilman and Nelson (39) on benzoyl chloride; however no reaction took place, presumably because of the ortho-bromine. Alkylation with methylmagnesium iodide gave a mixture of products which was not further investigated.

EXPERIMENTAL[6]

2-Bromobenzoyl chloride (38) was made in 95% yield from 2-bromobenzoic acid (Eastman) by means of thionyl chloride (refluxing for twenty-two hours); b.p. 120–126° (15 mm.); n_D^{20} 1.5965. When added to a large excess (twelve equivalents) of cold concentrated ammonium hydroxide it gave *2-bromobenzamide* in 97.6% yield; m.p. 159.5–161.5° [S. (38), 155–156°]. Refluxing with three equivalents of thionyl chloride for seventeen hours followed by steam distillation gave *2-bromobenzonitrile* in 84% yield; m.p. 52.5–54.5° [S. (40), 51°]. This nitrile reacted with three equivalents of methylmagnesium bromide to give *2-bromoacetophenone*, (69%), b.p. 131–135° (20 mm.) [B. and S. (37), 118–120° (16 mm.)]; n_D^{20} 1.5667–1.5678; semicarbazone, m.p. 175–177° [E., G., and J. (33), 177°].

α,2-Dibromoacetophenone was prepared in 73% yield by Procedure 1B; b.p. 104–127° (1.8 mm.), n_D^{20} 1.6040–1.6126.

Anal. Calc'd for $C_8H_6Br_2O$: C, 34.57; H, 2.18.
Found: C, 34.04; H, 2.16.

X. α-3-IODOPHENYL-β-DIALKYLAMINOETHANOLS

The 3-iodoacetophenone was made from 3-nitroacetophenone through the 3-amino derivative by diazotization (*cf.* section VI).

EXPERIMENTAL[6]

3-Iodoacetophenone (41) was obtained in 57% yield from 3-nitroacetophenone as follows: 109 g. (0.68 mole) of 3-nitroacetophenone was added in one portion (stirring) to 450 g. of stannous chloride dihydrate and 600 ml. of concentrated hydrochloric acid at 3–5°. The temperature was allowed to rise slowly and was maintained at 80–90° to complete the reduction. Cooling to 2–5° gave a pasty suspension to which about 300 ml. of water was added. A solution of 45 g. (0.66 mole) of sodium nitrite in 85 ml. of water was added slowly, delivered below the surface through a capillary, until a positive reaction in the starch-iodide test was obtained; the mixture was allowed to stand for fifteen minutes, and was treated with aqueous urea to destroy the excess nitrous acid. A solution of 2.9 g. (1.32 moles) of potassium iodide was added slowly; the mixture was allowed to warm to room temperature overnight, and then was heated on the water-bath until evolution of nitrogen ceased. The dark oil which separated was washed and distilled; 92 g. (57%), b.p. 102° (2 mm.) [E., M., and W. (41), 128.5° (8 mm.)]

α-Bromo-3-iodoacetophenone. (See Procedure 1A). Yield 75%. Recrystallized from methanol; m.p. 62–65°.

Anal. Calc'd for C_8H_6BrIO: C, 29.57; H, 1.86.
Found: C, 29.31; H, 2.07.

XI. THE α-2-IODOPHENYL-β-DIALKYLAMINOETHANOLS

The commercially available 2-iodobenzoyl chloride was used as the starting material rather than 2-aminoacetophenone (42). The α-bromomethyl ketone was obtained *via* the efficient path through the acid chloride and diazo ketone in an over-all yield of 70%.

EXPERIMENTAL[6]

α-Bromo-2-iodoacetophenone. A solution of 133.5 g. (0.5 mole) of 2-iodobenzoyl chloride in twice its volume of absolute ether was added slowly to 1.4 moles of diazomethane in

2 l. of ether which had previously been dried over potassium hydroxide (effervescence). After standing overnight, 219 ml. of 48% hydrobromic acid in an equal volume of ether was added; frothing occurred and an aqueous layer separated. After standing for two hours, the ether layer was separated, washed, dried, and concentrated. The resulting oil was vacuum distilled; 114 g. (70%), b.p. 140–143° (2 mm.). It was redistilled; b.p. 162–164° (6 mm.).

Anal. Calc'd for C_8H_6BrIO: C, 29.57; H, 1.86.
Found: C, 29.72; H, 1.90.

α-2-Iodophenyl-β-benzylmethylaminoethanol (*XId*), prepared according to Procedure 7SQ, was vacuum distilled; b.p. 197–200° (2 mm.) (55%). Evidence was observed of hydramine fission upon distillation and some benzylmethylamine hydriodide was obtained. Redistillation produced more of the fission products. Evaporating onto a cold-finger condenser at 95–100° (0.5 mm.) gave a sample which contained negligible amounts of fission products, as shown by failure to obtain a precipitate of more of the salt on dilution with ether.

XII. THE α-4-ALKOXYPHENYL-β-DIALKYLAMINOETHANOLS

The new *p*-butoxyacetophenone used as a starting material was prepared by a Friedel-Crafts reaction on butyl phenyl ether. The low yield (45%) may in part be explained by the formation of the by-product, 1,1-di-(*p*-butoxyphenyl)-ethylene, $(p\text{-}C_4H_9OC_6H_4)_2C=CH_2$, a considerable amount of which was isolated from the reaction mixture. This type of compound has been reported by Gattermann and co-workers (43, 44) in the preparation of *p*-methoxyacetophenone, and by Skraup and Nieten in the preparation of *p*-methoxybutyrophenone (45).

Bromination of the methyl ketones proceeded readily in ether and the resulting solutions were used without isolation of the bromomethyl ketones in the condensations with the amines.

EXPERIMENTAL[6]

α-Bromo-4-methoxyacetophenone had been prepared previously by bromination of 4-methoxyacetophenone in glacial acetic acid (46). In this investigation ether was used as the solvent according to Procedure 1. After crystallization from ethanol it melted at 69–71° (B. (46), 70–71°).

α-4-Methoxyphenyl-β-di-n-amylaminoethanol (*XIIa*). The crude amino alcohol was first evaporated *in vacuo* at 130–154° (3 mm.) and then purified according to Notes TS.

α-Bromo-4-ethoxyacetophenone was prepared according to Procedure 2 (not isolated).

4-Butoxyacetophenone. A mixture of 214 g. (1.43 moles) of butyl phenyl ether (47), 186 g. (2.37 moles) of acetyl chloride and one liter of dry carbon disulfide was cooled in an ice-bath and 230 g. (1.72 moles) of powdered anhydrous aluminum chloride was added gradually with stirring over a period of fifteen minutes. The ice-bath was removed and the mixture was stirred at room temperature for 7.5 hours and hydrolyzed with ice and hydrochloric acid. The carbon disulfide layer (the aqueous layer was extracted once with more carbon disulfide) was extracted six times with 6 *N* hydrochloric acid, washed with water, and dried over calcium chloride. The solvent was removed under reduced pressure and the crude residual ketone was vacuum distilled. The fraction boiling at 125–155° under 2 mm. pressure (yield 126 g.) was refractionated; b.p. 127–131° at 3 mm.; 120 g. (44%); n_D^{23} 1.5281–1.5290.

The *oxime* prepared in the usual way melted at 86° after repeated crystallization from 60–80% ethanol.

Anal. Calc'd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27.
Found: C, 69.21; H, 8.34.

1,1-Di-(4-butoxyphenyl)ethylene. The residue remaining in the flask after the first distillation of the crude 4-butoxyacetophenone was crystallized from ethanol after Norit treatment; white plates; m.p. 125–126°; yield 34.2 g. (15%). A sample after four crystallizations from ethanol melted at 127°.

Anal. Calc'd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70.

Found: C, 81.77; H, 8.83.

α-Bromo-4-butoxyacetophenone was prepared according to Procedure 2 (not isolated).

XIII. THE α-4-ALKYLPHENYL-β-DIALKYLAMINOETHANOLS

Bromination of the methyl ketones, namely 4-*n*-hexyl-, 4-*n*-decyl-, and 4-*n*-dodecyl-acetophenones, proceeded easily in ether solution; the bromomethyl ketones were not isolated before condensation with the amines; and aluminum isopropoxide reduction of the crude amino ketones (also not isolated) proceeded without complications, except in the case of α-4-dodecylphenyl-β-diethylaminoethanol, where hydramine fission apparently interfered to some extent in the purification of the product by distillation under reduced pressure. The failure of dicylohexylamine to react with 4-isopropylphenacyl bromide in the usual way was also noted.

EXPERIMENTAL[6]

The 4-n-hexyl, 4-n-decyl, and 4-n-dodecylacetophenones were supplied by the OSRD group at Columbia University under Dr. Elderfield.

4-Cyclohexylacetophenone was prepared from phenylcyclohexane by the method of Mayes and Turner (48). It was found that fractional distillation of the crude ketone under reduced pressure gave a purer product than that obtained on crystallization. The 4-cyclohexylacetophenone used boiled at 165–173° (10 mm).

α-4-Hexylphenyl-β-di-n-amylaminoethanol (*XIIIc*) was first distilled at 4 mm. The fraction distilling at 155–225° was fractionated at 2 mm. The fraction distilling at 206–216° was then fractionally evaporated onto a cold-finger condenser under reduced pressure.

α-4-n-Decylphenyl-β-di-n-butylaminoethanol (*XIIIg*) was vacuum evaporated at 133–155° (2 mm.), redistilled (233-242°, 3 mm.), and then again vacuum evaporated.

α-4-n-Dodecylphenyl-β-diethylaminoethanol (*XIIIh*) was subjected to two vacuum distillations and one vacuum evaporation without obtaining an analytically pure sample. Since nitrogen analysis of the product was low, hydramine fission was suspected to have occurred to some extent.

XIV. α-4-BENZYLPHENYL-β-DI-*n*-BUTYLAMINOETHANOL

The procedure for the preparation of the starting material, 4-acetyldiphenylmethane (49), was modified somewhat to achieve the best results, and involved the slow addition of a mixture of approximately equimolar quantities of diphenylmethane and acetyl chloride to a mechanically stirred mixture of aluminum chloride and carbon disulfide. 4,4′-Diacetyldiphenylmethane (49) was also isolated as a by-product.

EXPERIMENTAL[6]

Preparation of 4-acetyldiphenylmethane and 4,4′-diacetyldiphenylmethane (49). A mixture of 168 g. (1.0 mole) of diphenylmethane and 80 g. (1.02 moles) of acetyl chloride was added dropwise to a mechanically stirred mixture of 175 g. (1.32 moles) of anhydrous aluminum chloride in 300 ml. of dry carbon disulfide at 0°. Upon completion of the addition the reaction mixture was allowed to warm to room temperature, and was poured into a mixture of 3 l. of ice and 50 ml. of concentrated hydrochloric acid. The products were extracted with carbon disulfide and fractionated under reduced pressure. The first fraction, boiling up to 135° (3.5 mm.), consisted largely of diphenylmethane; 73 g.; the second fraction was crude 4-acetyldiphenylmethane; b.p. 135–190° (2–2.5 mm.); 41 g. (34% allowing for the recovery of diphenylmethane). A pure sample was obtained from material boiling at 162–184.5° (5 mm.) by recrystallizing from ethanol; m.p. 38–39° (D., 39°). The 4,4'-diacetyldiphenylmethane was isolated by recrystallizing the material boiling at 240–245° (6 mm.) from ethanol; m.p. 92.5–93° (D., 93°).

When acetyl chloride (1 mole) was added slowly to a mixture of diphenylmethane (1.5 moles), anhydrous aluminum chloride (1.5 moles) and carbon disulfide at 0°, only a 25% yield of the crude 4-acetyldiphenylmethane was obtained, together with small amounts of acetophenone (49) and 4,4'-diacetyldiphenylmethane.

4,4'-Bis(bromoacetyl)diphenylmethane was prepared according to Procedure 1A; yield 97%. Several recrystallizations from isopropanol and from butanone-ligroin gave a product of m.p. 137.5–138.5°.

Anal. Calc'd for $C_{17}H_{14}Br_2O_2$: C, 49.78; H, 3.44.
Found: C, 49.63; H, 3.95.

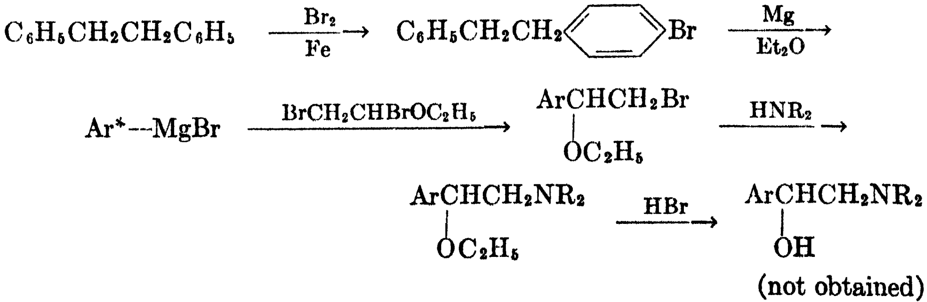
Attempted preparation of 4,4'-bis(2-di-n-butylamino-1-hydroxyethyl)diphenylmethane according to Procedure 3G and 5R resulted in considerable decomposition, and no tractable product was obtained.

4-(β-Diethylaminopropionyl)diphenylmethane hydrochloride (XIVB) was made by a typical Mannich reaction on 4-acetyldiphenylmethane (refluxing for 53 hours in ethanol) (see Sections II and III).

XV. α-4-(2-PHENYLETHYL)PHENYL-β-DI-*n*-BUTYLAMINOETHANOL

Two reaction paths were studied, one of these successfully. A representative amino alcohol in this series was prepared through 4-acetylbibenzyl which was obtained through the Friedel-Crafts reaction between bibenzyl and acetyl chloride in carbon disulfide. The 4-acetylbibenzyl was converted in the usual way, by α-bromination, condensation with dibutylamine, followed by aluminum isopropoxide reduction, into the amino alcohol.

An unsuccessful attempt was made to adopt the scheme followed by Späth and Göhring in the synthesis of ephedrine (50) as is illustrated in the following diagram; failure was experienced in the last step.



Ar* = 4 = (2 = phenylethyl)phenyl.

The Grignard reagent from bromobibenzyl was condensed with α,β-dibromoethyl ethyl ether (*cf.* Ref. 50) in 53% yield, and the resulting β-bromo ether was condensed with diethylamine, giving an 82% yield of the pure dialkylaminoethyl derivative (as the hydrochloride). Repeated attempts to hydrolyze this ether to the desired amino alcohol according to the method of Späth and Göhring (50) resulted only in the formation of resinous products.

The α-(4-bibenzyl)-β-diethylaminoethyl ethyl ether hydrochloride was tested against avian malaria and was found to be inactive.

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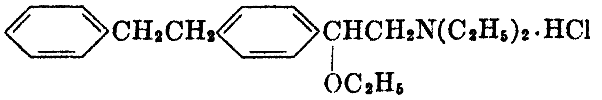


$C_6H_5CH_2CH_2C_6H_4CH(OC_2H_5)CH_2N(C_2H_5)_2\cdot HCl$

$Q = < 0.3$

EXPERIMENTAL[6]

4-Acetylbibenzyl. A suspension of 533 g. (4 moles) of aluminum chloride and 364 g. (2 moles) of bibenzyl in 750 ml. of dry carbon disulfide was vigorously stirred and cooled to 0°. Acetyl chloride (157 g., 2 moles) was added at such a rate as to maintain the temperature between 0–5°. The mixture was stirred overnight and poured onto ice and hydrochloric acid. The solid which was formed was filtered (54 g.); this was the diacetyl compound (see below). The carbon disulfide layer upon drying and concentrating gave a lower-melting solid which was crystallized from ethanol and fractionally distilled under a pressure of 3 mm. The fraction distilling at 172–173° weighed 277 g.; m.p. 68–70°. An analytical sample was prepared by three crystallizations from methanol.

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.67; H, 7.19.
Found: C, 85.58; H, 6.89.

4,4'-Diacetylbibenzyl. The solid (54 g.) which was filtered from the carbon disulfide layer from the above experiment, was purified by repeated crystallizations from absolute ethanol; m.p. 167–168°.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81.
Found: C, 81.48; H, 6.62.

α-Bromomethyl-4-bibenzyl ketone was prepared by bromination of 4.5 g. of 4-acetylbibenzyl according to Procedure 1A. The product (3.6 g.) was crystallized several times from ligroin; m.p. 61°.

Anal. Calc'd for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99.
Found: C, 63.80; H, 4.95.

α-4-(2-Phenylethyl)phenyl-β-di-n-butylaminoethanol hydrochloride (XVA). An aliquot portion (0.2 mole) of bromomethyl 4-bibenzyl ketone was reacted with 0.4 mole of di-*n*-butylamine according to Procedure 3F. Reduction to the amino alcohol was effected by Procedure 5Q using 200 ml. of 3 *N* aluminum isopropoxide under five hours of heating. Purification was difficult and six crystallizations from ethyl acetate and six from water were required to obtain an analytical sample.

4-Bromobibenzyl (51, 52). A mixture of 728 g. (4 moles) of bibenzyl and 8 g. of iron filings under a reflux condenser and under efficient stirring, was treated dropwise and without heating with 640 g. (4 moles) of bromine over a period of 1.5 hours. Hydrogen bromide was evolved briskly as the temperature rose. After the addition was completed, the dark red mixture was heated for three hours under stirring, and allowed to stand overnight; it was then stirred and treated with 350 ml. of 10% sodium hydroxide (30 min.), and washed with water. The resulting yellow oil was distilled; 444 g. (43%); b.p. 141–145° (3 mm.); 150 g. of unreacted bibenzyl was recovered from the lower-boiling portion of the distillate (118–120° at 3 mm.); and allowing for this recovery of starting material the yield of product was 63%, calculated from the bibenzyl consumed.

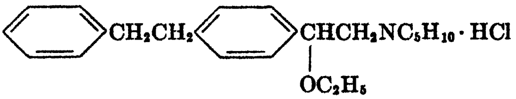
4-(β-Diethylamino-α-ethoxyethyl)bibenzyl hydrochloride. An ice-cold solution of bibenzylmagnesium bromide (prepared in the usual way from 0.1 mole of 4-bromobibenzyl) was treated slowly with 23.2 g. (0.1 mole) of α,β-dibromoethyl ethyl ether (53) and the mixture was stirred for twenty-two hours. The resulting dark brown mixture was poured onto ice (acidified). The ether layer was separated, and the water layer was extracted several times with ether. The combined ether extract was dried over sodium sulfate, concentrated, filtered from a small amount of solid, and evaporated; the residual oil was fractionally distilled. The fraction distilling at 183° (5 mm.) weighed 10 g. (31%).

On a much larger scale, using 540 ml. of 1.3 *N* bibenzylmagnesium bromide (0.71 mole) and 0.72 mole of α, β-dibromoethyl ethyl ether, and slowly adding the Grignard reagent to the dibromo ether and stirring for forty-eight hours at room temperature, a 53% yield of distilled product was obtained.

Fifty grams (0.15 mole) of this product was condensed with 43.7 g. (0.6 mole) of diethylamine by heating the mixture under reflux for eight hours and allowing it to stand at 50° for fifty-six hours. The diethylamine hydrobromide (11.2 g.; 72%) was filtered, and the ethereal filtrate was washed and dried. The hydrochloride of the product was precipitated by the addition of ethereal hydrogen chloride, and it was recrystallized from ethyl acetate; 45 g. (82%); m.p. 131–132°. The melting point after several recrystallizations was 132.5–133°.

Anal. Calc'd for $C_{22}H_{31}NO \cdot HCl$: C, 72.98; H, 8.91.
Found: C, 72.94; H, 8.87.

4-(β-Piperidyl-α-ethoxyethyl)bibenzyl hydrochloride.



A mixture of 10 g. (0.03 mole) of α-(4-bibenzyl)-β-bromoethyl ethyl ether and 5.2 g. (0.06 mole) of piperidine in 45 ml. of ether was heated under reflux for twenty-four hours, and was allowed to stand for twelve hours at room temperature. A 44% yield of piperidine hydrobromide was removed. The residue obtained upon evaporation of the ethereal filtrate was dissolved in acetone, and the hydrochloride was precipitated by addition of ethereal hydrogen chloride. Dilution with ether, cooling, and filtration produced 2.1 g. of product (19%); m.p. 167–170°. After several crystallizations from ethyl acetate it melted at 170–170.5°.

Anal. Calc'd for $C_{23}H_{31}NO \cdot HCl$: C, 73.88; H, 8.63.
Found: C, 73.98; H, 8.59.

XVI. THE α-(4-CHLORO-3-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

EXPERIMENTAL[6]

4-Chloro-3-methylacetophenone was prepared according to Noller and Adams (54) by the Friedel and Crafts acylation of ortho-chlorotoluene. *α-Bromo-4-chloro-3-methylacetophenone* was made from it by Procedure 1A, and was isolated and characterized, but the amino ketone and two amino alcohols were prepared directly from aliquot portions of ethereal solution of the crude α-bromomethyl ketone. The α-bromomethyl ketone was isolated in 69% yield by evaporating the reaction solvent and recrystallizing from ethanol; colorless rectangular rods; m.p. 56–57°.

Anal. Calc'd for C_9H_8BrClO: C, 43.67; H, 3.26.
Found: C, 43.51; H, 2.95.

α-(4-Chloro-3-methylphenyl)-β-di-n-amylaminoethanol (*XVIAa*) was prepared by the reaction between the bromomethyl ketone, diamylamine, and aluminum isopropoxide (in one operation) as described under IIAh(b).

α-(4-Chloro-3-methylphenyl)-β-di-n-octylaminoethanol (*XVIAb*). To an aliquot portion (0.1 mole) of the ethereal solution of the α-bromomethyl ketone was added 49 g. (0.2 mole) of dioctylamine. Procedures 3K and 5R were followed, with two vacuum distillations, and the product was obtained as a pale yellow oil.

α-Benzylmethylamino-4-chloro-3-methylacetophenone hydrochloride (XVIB). A mixture of an aliquot portion (0.3 mole) of the ethereal solution of the α-bromomethyl ketone and 72.8 g. (0.6 mole) of benzylmethylamine was worked up according to Procedure 3L. Repeated crystallizations gave the pure product as bundles of colorless needles.

α-(4-Chloro-3-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (XVIAc). A mixture of 16.2 g. (0.05 mole) of the amino ketone hydrochloride, 200 ml. of dry isopropanol and 80 ml. of 3 *N* aluminum isopropoxide was treated according to Procedure 6Q. The amino alcohol hydrochloride was precipitated from dry ether by etheral hydrogen chloride and was recrystallized from absolute ethanol-ether as colorless needles.

XVII. THE α-(3-CHLORO-4-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

3-Chloro-4-methylacetophenone (*cf.* 55) needed for the preparation of these compounds, was made in a new way through nitration of 4-methylacetophenone, stannous chloride reduction, diazotization, and the Sandmeyer reaction.

EXPERIMENTAL[6]

Preparation of 4-methyl-3-nitroacetophenone followed the nitration procedure described in Section VI except that the reaction temperature was maintained just under −15° (*cf.* 56). The crude product was a very pale yellow solid; yield 94% of m.p. 54–57°; recrystallization from ethanol gave a product of m.p. 60–61° (80%) (F., 61°). It could also be crystallized from ligroin.

Preparation of 3-chloro-4-methylacetophenone. The 4-methyl-3-nitroacetophenone prepared as above was reduced to the amino compound (which was not isolated) and was converted through the diazonium salt to the chloro compound, applying the "Organic Syntheses" (31) directions for making 3-chlorobenzaldehyde, and using 118 g. (0.66 mole) of 4-methyl-3-nitroacetophenone. Just prior to the diazotization, 300 ml. of acetic acid was added to serve as a solvent (this was done because in a trial run in which acetic acid was not used, considerable nitrous acid was lost, apparently because most of the compound being diazotized was present as a precipitate and was slow to dissolve). An excess of sodium nitrite [66 g. (0.96 mole) in 200 ml. of water] was added over six hours and the excess nitrite was destroyed by adding 13 g. (0.22 mole) of urea in 25 ml. of water. Upon standing overnight the product crystallized; it was filtered and recrystallized, twice from ethanol and once from ligroin; yield 60 g. (53%); m.p. 44–45° [W. and L. (55), 45–46°].

α-Bromo-3-chloro-4-methylacetophenone (not isolated). Ninety grams (0.56 mole) of bromine was added during a period of ninety minutes under stirring to 90 g. (0.53 mole) of the ketone in 500 ml. of petroleum ether (b.p. 35–60°); the mixture was then refluxed (water-bath at 50°) for four hours, when the evolution of hydrogen bromide had practically ceased; the remaining mixture was concentrated to 133 g. under reduced pressure. Since cooling in ice failed to yield a crystalline product, the residual dark liquor was dissolved in 300 ml. of acetone, treated with Darco, dried over sodium sulfate, filtered, and made up to a volume of 500 ml. with additional acetone. This solution was assumed to contain 0.44 mole of the bromomethyl ketone, and aliquots were reacted directly under nitrogen with two equivalents of the appropriate amine.

α-(3-Chloro-4-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (XVIIAc) was made by Procedures 3L and 6Q; white needles. The intermediate amino ketone was isolated as the hydrochloride (see Table I), and a mixture melting point with XVIIAc resulted in a 15° depression.

XVIII. THE α-(2-CHLORO-4-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

2-Chloro-4-methylacetophenone, as starting material for the preparation of compounds in this series, was originally prepared in yields of approximately 50%, using the Friedel and Crafts reaction between acetyl chloride and 3-chlorotoluene

(57, 58; *cf.* also 59). In the present investigation acetic anhydride was used instead of acetyl chloride (54). Permanganate oxidation of the acetylation product to chloroterephthalic acid indicated that the reaction had given chiefly the desired compound. However, it must be assumed that the product obtained here was not entirely free from the structural isomer. Work was started toward the synthesis of a pure sample from 2-chloro-4-methylaniline through the nitrile but was postponed because the sample of the diamylamino alcohol already submitted for avian malaria screening tests, although active, was only one-third as active as quinine.

EXPERIMENTAL[6]

Preparation of 2-chloro-4-methylacetophenone. The method of Noller and Adams (54) was adapted to the preparation of this starting material. A 54% yield of the colorless liquid was obtained; b.p. 97–99° (4 mm.) or 239–241° (740 mm).

Permanganate oxidation of 5 g. of this ketone according to the method of Ganguly and Le Fèvre (58) yielded 4 g. of chloroterephthalic acid; m.p. 315°. One recrystallization from water gave the colorless acid of m.p. 316–317° (G. and Le F., 320°).

α-(2-Chloro-4-methylphenyl)-β-di-n-amylaminoethanol (XVIIIa). A mixture of an aliquot portion (0.1 mole) of the α-bromomethyl ketone solution and 32 g. (0.203 mole) of diamylamine was treated according to Procedures 3K and 5R (two vacuum fractionations). Evidence for the loss by displacement of some of the ortho halogen was obtained during the fractionations (*cf.* Section III); a significant quantity of diamylamine hydrochloride was isolated.

α-(2-Chloro-4-methylphenyl)-β-benzylmethylaminoethanol (XVIIIb). To an aliquot portion (0.2 mole) of the α-bromomethyl ketone solution was added 48.4 g. (0.4 mole) of benzylmethylamine; the reaction mixture was worked up according to Procedure 3L.

Reduction of 16 g. of the amino ketone hydrochloride by 200 ml. of 1.5 *N* aluminum isopropoxide was carried out according to Procedure 6R. The vacuum fractionation was carried out under an atmosphere of nitrogen, using a heated fractionating column.

XIX. THE α-(2-CHLORO-5-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

In the synthesis of this series of compounds an interesting observation was made. Reduction of the crude dioctylaminomethyl ketone in the form of the free base (not isolated) failed to yield a pure sample of the amino alcohol; however, when anhydrous aluminum chloride was added to the reduction mixture to furnish chloride ion, a satisfactory product was obtained. This result is to be compared with the observation (12) that the aluminumi sopropoxide reductions of the 4-bromo-α-dialkylaminoacetophenone hydrochlorides proceed in much better yields than the reduction of the free bases.

EXPERIMENTAL

2-Chloro-5-methylacetophenone was prepared according to Allen and Bridges (60) through the Friedel-Crafts reaction between acetic anhydride and 4-chlorotoluene.

α-Bromo-2-chloro-5-methylacetophenone was prepared according to Procedure 2 and was used without isolation.

α-(2-Chloro-5-methylphenyl)-β-di-n-octylaminoethanol (XIXa). An aliquot portion (0.6 mole) of the α-bromomethyl ketone and 289.5 g. (1.2 moles) of dioctylamine was treated according to Procedure 3K. The crude amino ketone (free base) (an oil) was dissolved in the reduction mixture and 40 g. (0.3 mole) of anhydrous aluminum chloride was added. The reaction was completed according to Procedure 9SR.

α-(2-Chloro-5-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (*XIXb*). A mixture of an aliquot portion (0.2 mole) of the α-bromomethyl ketone solution and 48.4 g. (0.4 mole) of benzylmethylamine was worked up according to Procedure 3L. Thirty grams of the amino ketone hydrochloride (obtained after crystallization from absolute ethanol-ether) was treated with 300 ml. of 1 *N* aluminum isopropoxide and the experiment was completed according to Procedure 6Q. The amino alcohol hydrochloride was precipitated from dry ether by ethereal hydrogen chloride; colorless rectangular rods.

XX. THE α-(3-CHLORO-4-ETHOXYPHENYL)-β-DIALKYLAMINOETHANOLS

These compounds were prepared from *o*-chlorophenetole through the Friedel and Crafts reaction with chloroacetyl chloride followed by condensation of the product with secondary amines. In order to make certain that the side chain had entered the 4-position as expected, the product was degraded by oxidation and reduction to 4-ethoxybenzoic acid.

EXPERIMENTAL[6]

α,3-Dichloro-4-ethoxyacetophenone. The procedure followed here approximates standard practice [see Jörlander (61)]. Fifty grams (0.38 mole) of finely powdered aluminum chloride was added during thirty minutes to a rapidly-stirred mixture of 38 g. (0.33 mole) of chloroacetyl chloride and 52 g. (0.33 mole) of *o*-chlorophenetole dissolved in 100 ml. of carbon disulfide. After standing for another hour, the resulting thin syrup was poured with stirring into 500 ml. of ice-water containing 20 ml. of concentrated hydrochloric acid. The product was isolated by concentrating the carbon disulfide layer under reduced pressure; colorless needles, m.p. 58–60°, yield 30 g. (56% of the theoretical, allowing for 17 g. of *o*-chlorophenetole that was recovered by fractional distillation of the filtrate). Carrying out this reaction at an elevated temperature, or using more aluminum chloride, resulted in a lower yield of the desired product and the formation of much tar.

A pure sample of the compound was obtained by recrystallizations from petroleum ether; m.p. 78°.

Anal. Calc'd for $C_{10}H_{10}Cl_2O_2$: C, 51.52; H, 4.32.

Found: C, 51.28; H, 4.14.

3-Chloro-4-ethoxybenzoic acid. A small sample of the α,3-dichloro-4-ethoxyacetophenone was oxidized in an excess of sodium hypochlorite solution at room temperature and was recrystallized from 50% ethanol; colorless prisms, m.p. 210°.

Anal. Calc'd for $C_9H_9ClO_3$: C, 53.88; H, 4.52.

Found: C, 53.53; H, 4.54.

Reduction in alkaline solution with nickel-aluminum alloy (Raney catalyst powder) gave *4-ethoxybenzoic acid*; m.p. 194–195° [L. and B. (62), 195°].

α-(3-Chloro-4-ethoxyphenyl)-β-diethylaminoethanol hydrochloride (*XXAa*) was prepared according to Procedures 3HK and 5Q, using four equivalents of diethylamine, with petroleum ether (b.p. 30–65°) as the solvent; the mixture was allowed to stand overnight and was then refluxed for six hours to hasten the condensation.

α-(3-Chloro-4-ethoxyphenyl)-β-benzylmethylaminoethanol hydrochloride (*XXAc*) was prepared according to Procedures 3L and 6Q as colorless tablets. A mixture melting point of this and the hydrochloride of the amino ketone from which it was prepared resulted in a 15° depression.

XXI. α-(5-CHLORO-2-METHOXYPHENYL)-β-DIAMYLAMINOETHANOL

The first approach to this series, the acylation of 4-chloroanisole by the Friedel and Crafts reaction, following essentially the procedure of Wittig (63), and then brominating the product according to Procedure 2, was unsuccessful. The second and successful approach consisted of condensing 4-chloroanisole with chloroacetyl chloride by the Friedel and Crafts reaction, under conditions which were essentially those employed by Jörlander (61); the condensation with diamylamine proceeded without difficulty and the resulting amino ketone was reduced to the amino alcohol in good yield.

EXPERIMENTAL

α-(5-Chloro-2-methoxyphenyl)-β-di-n-amylaminoethanol hydrochloride (*XXI*) was prepared according to Procedures 3JK and 5RQ, using 0.1 mole of α,5-dichloro-2-methoxyacetophenone [see Jörlander (61)] in 100 ml. of acetone. After adding the amine, it was found advantageous to replace the air in the flask with nitrogen. Acetone, rather than ether, was used in this step because the by-product diamylamine hydrochloride precipitated from this solvent as larger and more easily filterable crystals.

After purifying, the amino alcohol (pale yellow oil) was converted into the hydrochloride (white needles) by dissolving it in ether and adding ethereal hydrogen chloride.

XXII. THE α-(4-BROMO-3-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

The starting material, 4-bromo-3-methylacetophenone, was prepared from 2-bromotoluene and acetic anhydride exactly according to the directions of Noller and Adams (54) for the Friedel-Crafts reaction on 2-chlorotoluene, and it was identified by conversion into the oxime, which showed the same melting point as that reported by Borsche and Herbert (64, *cf.* also 59).

EXPERIMENTAL[6]

Preparation of 4-bromo-3-methylacetophenone. Careful fractionation gave a 45% yield of colorless oil; b.p. 119–125° (4–5 mm.); n_D^{20} 1.5738 ±5. Forty-six per cent of the starting material was recovered.

The *oxime* (64), colorless needles, precipitated slowly from ethanol; yield 60%; m.p. 108–109° (B. and H., 108°).

α,4-Dibromo-3-methylacetophenone was prepared according to Procedure 1D; colorless oil; yield 38%; b.p. 156–164° (1–2 mm.); n_D^{20} 1.6130 (not analyzed).

XXIII. α-(4-BROMO-2-METHYLPHENYL)-β-DI-*n*-AMYLAMINOETHANOL

The preparation of this compound was based on the Friedel-Crafts synthesis of the 4-bromo-2-methylacetophenone from 3-bromotoluene and acetic anhydride, following exactly the procedure of Noller and Adams (54) for making 4-chloro-3-methylacetophenone from 2-chlorotoluene. The identity and homogeneity of the sample of the acetylation product made in this investigation was not established; it is assumed that the orientation in the Friedel-Crafts reaction was in the main the same as in the original preparation by Claus (59, *cf.* also 64) using acetyl chloride.

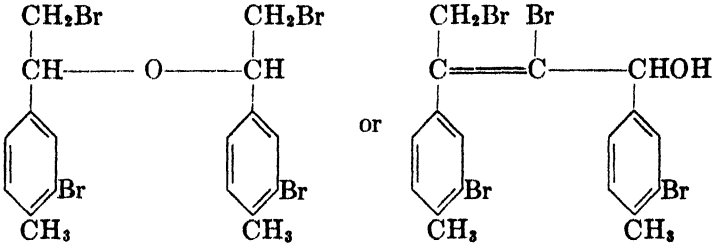
EXPERIMENTAL

α-(4-Bromo-2-methylphenyl)-β-di-n-amylaminoethanol (*XXIII*) was evaporated under reduced pressure onto a cold-finger condenser and then fractionally distilled under reduced pressure and an atmosphere of nitrogen, using a heated column. The product was a pale yellow oil.

XXIV. THE α-(3-BROMO-4-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

This synthesis utilized 3-amino-4-methylacetophenone (65), which was obtained from the nitro compound by reduction with stannous chloride. The Sandmeyer reaction gave the desired 3-bromo-4-methylacetophenone, which was readily brominated, and converted by aluminum isopropoxide reduction into the bromohydrin.

In the latter reaction a by-product was obtained, which from the analysis may be either of the following, the bromohydrin ether, or the product of an aldol condensation between two bromo ketone molecules and reduction of the remaining carbonyl (*cf.* Ref. 8).



There is analogy in the literature for both of these type reactions under the influence of aluminum isopropoxide (*cf.* Ref. 8). However, in the case of aldol condensation, steric hindrance would be expected to be insurmountable, and leads us to favor the former structure.

EXPERIMENTAL[6]

3-Amino-4-methylacetophenone. Reduction (*cf.* Ref. 31) of 66 g. of the 3-nitro compound (made as in Section XVII) by 1.2 moles of diaquo stannous chloride in 400 ml. of 1.2 *N* hydrochloric acid (slow heating) produced a sudden temperature rise from 43° to 70°, and a cooling bath was applied to check the reaction and to hold it at 70°.Heat was then applied to maintain the temperature at 65–70° for half an hour. Treatment with alkali gave 50 g. (92%); m.p. 77–79° (B. and D., 80°).

3-Bromo-4-methylacetophenone was obtained in 62% yield, following a procedure similar to that in "Organic Syntheses" (66a). Small-scale runs gave the better results. The product from steam distillation solidified (m.p. 41–43°) and after two crystallizations from 70% ethanol melted at 43°; rhombic plates.

Anal. Calc'd for C_9H_9BrO: C, 50.73; H, 4.26.
Found: C, 50.39; H, 4.56.

α,3-Dibromo-4-methylacetophenone was made in nearly quantitative yield by Procedure 1. After several crystallizations from ethanol it melted at 67–68°.

Anal. Calc'd for $C_9H_8Br_2O$: C, 37.02; H, 2.76.
Found: C, 36.85; H, 2.92.

α-Bromomethyl-3-bromo-4-methylbenzyl alcohol. (*cf.* Procedure 10). The reduction time was 10 minutes. The product distilled at 162–171° (3 mm.) and solidified; m.p. 47–49° (87%). Two crystallizations from ethanol and one from ligroin raised the melting point to 50°.

Anal. Calc'd for $C_9H_{10}Br_2O$: C, 36.76; H, 3.43.
Found: C, 36.79; H, 3.41.

A second reduction (one hour instead of 10 minutes) gave a 70% yield of the bromohydrin and a higher-boiling compound which was crystallized repeatedly from ethanol; m.p. 136–137°.

Anal. Calc'd for $C_{18}H_{18}Br_4O$: C, 38.06; H, 2.87.
$C_{18}H_{16}Br_4O$: C, 37.93; H, 3.18.
Found: C, 38.14; 38.04; H, 3.29; 3.59.

The di-n-butylamino alcohol (*XXIVa*) (Procedure 11RQ; condensation at 94° for 10 hours) distilled at 185–198° (2 mm.), and was converted into the hydrochloride from ether and recrystallized from a petroleum ether-acetone mixture by addition of ether. The *di-n-octylamino compound* (XXIVb) (Procedure 11R; condensation at 94° for 9 hours) was fractionally distilled (b.p. 262–272° at 2 mm.) and molecularly distilled twice at 135–140° under 10^{-3} mm. The hydrochloride (from ether) was extremely hygroscopic; it was recrystallized from ether (heating under pressure to dissolve).

XXV. THE α-3,4-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

The amino alcohols, except the dicyclohexylamino compound, were prepared without difficulty by aluminum isopropoxide reduction of the amino ketones. When an attempt was made to prepare the dicyclohexylamino alcohol by the condensation with dicyclohexylamine, a reaction occurred with the formation of 70% of the theoretical amount of dicyclohexylamine hydrobromide; however, aluminum isopropoxide reduction of the resulting crude mixture gave none of the desired amino alcohol, and only dicyclohexylamine was isolated. The condensation with dicylohexylamine was effected, finally, through the bromohydrin, and this produced the desired amino alcohol directly, although in only 19% yield. The very low yield by this usually excellent method, and the absence of significant amounts of resinous by-products, is accounted for by assuming that the reaction proceeded first to the oxide, and that this conversion was complete and rapid, whereas the subsequent condensation of the secondary amine with the oxide to the amino alcohol was slow and incomplete in the time involved; the unreacted oxide, unexpected when this experiment was carried out, was undoubtedly lost in the vacuum distillation of the final product. The results of the reaction between dicyclohexylamine and α-bromomethyl-6,8-dichloro-2-phenyl-4-quinoline-methanol, where the oxide was formed and isolated under similar conditions (10), supports this conclusion.

EXPERIMENTAL[6]

α-Bromomethyl-3,4-dichlorobenzyl alcohol was prepared according to Procedure 10Z; it was crystallized from ligroin; 87% yield; m.p. 59–60°.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.
Found: C, 36.06; H, 2.54.

α-3,4-Dichlorophenyl-β-n-octylaminoethanol hydrochloride (*XXVAh*) was prepared according to the Procedure 11T by heating a solution of 57.3 g. (0.44 mole) of monooctylamine and 30 g. (0.11 mole) of the bromohydrin in 175 ml. of dry toluene at 70–90° for nine hours. The mixture was then refluxed for seven hours. The toluene was removed by distillation under reduced pressure, and 300 ml. of absolute ether was added to the residue. The *n*-octylamine hydrobromide which separated was filtered; 23.3 g. (100%). The ether filtrate was extracted with four 250-ml. portions of 1 *N* hydrochloric acid and then with 200 ml. of water. The ether layer containing the hydrochloride was separated and cooled to 0°, and the white salt which then precipitated was filtered and dried. Two crystallizations from acetone gave 22 g. (56%); m.p. 227–229° dec.

α-3,4-Dichlorophenyl-β-dicyclohexylaminoethanol hydrochloride (*XXVAi*). Procedure 11Q was used. The light yellow oil which remained after evaporation of the ether was transferred to a small Claisen flask, and all of the material which was volatile below 100° at a pressure of 1 mm. (doubtless including 3,4-dichlorophenyl ethylene oxide) was distilled. In order effectively to remove all traces of dicyclohexylamine, 15 ml. of diphenyl ether was added to the residual oil, and the distillation was repeated. The crude hydrochloride which precipitated from ether was crystallized from ethyl acetate and then from 30:70 acetone-ligroin.

XXVI. THE α-2,4-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

Several paths to the starting material, 2,4-dichloroacetophenone, were investigated. The Friedel-Crafts reaction on *m*-dichlorobenzene appeared to be impractical (67a). The action of methylmagnesium iodide on the 2,4-dichlorobenzoyl chloride, in spite of steric hindrance, which was expected to slow down somewhat the secondary reaction, gave a mixture of products, as also did dimethylcadmium. The synthesis was best accomplished through the nitrile by the addition of methylmagnesium iodide, and the yields in all of the steps starting from the acid chloride and going through the amide to the nitrile, were good except for the last step involving the addition of the Grignard reagent, where only a 25% yield was realized. The conversion from this point to the amino alcohols was accomplished through the bromo ketone and bromohydrin, which were obtained in good yields.

EXPERIMENTAL[6]

2,4-Dichlorobenzamide was obtained in 96% yield by the action of ice-cold aqueous ammonium hydroxide on the acid chloride; recrystallized from ethanol; m.p. 193–194°.

Anal. Calc'd for $C_7H_5Cl_2NO$: C, 44.24; H, 2.65.

Found: C, 44.20; H, 2.65.

2,4-Dichlorobenzonitrile, made originally from 2,4-dichloroaniline by the Sandmeyer reaction (68), was made here in 96% yield by the action of an excess of thionyl chloride on the amide (refluxing for eight hours); recrystallized from petroleum ether; m.p. 61–62° (G. and C., 61°).

A new preparation of 2,4-dichloroacetophenone. An ether solution (1.5 l.) of 188 g. (1.1 moles) of the above nitrile was added over five hours to 1.5 l. of ethereal 2.25 *N* methylmagnesium iodide (3.4 moles) under reflux, refluxing was continued for twelve hours, and the ether distilled. The reaction mixture was hydrolyzed by addition of 70 ml. of water and then 1270 g. of 77% sulfuric acid, breaking up the solid mass, refluxing for a short time, standing for twelve hours, again refluxing for a short time, and allowing to stand for an additional thirty-six hours; this was followed by addition of water and extraction of the product with ether. Fractional distillation under 22 mm. pressure gave 49 g. (25%) boiling at 132–135°; m.p. 30° [R. and T. (67), 33–34°]. The over-all yield from the acid was 16%.

α-Bromomethyl-2,4-dichlorobenzyl alcohol. A solution of 65.1 g. of the ketone in 250 ml. of absolute ether was brominated by adding 55 g. of bromine and moderating the temperature by a cooling bath as the reaction proceeded (over a half hour). After washing the solution with water and sodium bicarbonate, drying over sodium sulfate and distilling off the ether, the residue of crude bromo ketone (88 g.) was reduced with 310 ml. of 3 *N* aluminum isopropoxide (Procedure 10Y) (refluxing for twenty-two hours). The product obtained from hydrolysis with 6 *N* sulfuric acid (87 g. of m.p. 53–56°) was recrystallized repeatedly from 80% ethanol (with Darco treatments); m.p. 72°.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.
Found: C, 35.38; H, 2.48.

α-2,4-Dichlorophenyl-β-di-n-octylaminoethanol hydrochloride (*XXVIb*), was obtained by Procedure 11, with heating at 100° for twenty minutes and 140° for three hours. The excess dioctylamine was eliminated from an ether solution by fractional precipitation with standard ethereal hydrogen chloride; upon acidification by an excess of ethereal hydrogen chloride, the product crystallized very slowly on standing in the ice-box.

XXVII. THE α-2,5-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

Lack of success in repeating the preparation of the starting material, 2,5-dichloroacetophenone, by the Friedel-Crafts reaction on *p*-dichlorobenzene (69), led to the development of an alternative method starting from 2,5-dichloroaniline through the Sandmeyer reaction to 2,5-dichlorobenzonitrile, essentially according to the method of Noelting and Kopp (70), and treatment of the nitrile with methylmagnesium iodide. We verified Noelting and Kopp's observation that successful diazotization depends upon strongly acid conditions and that the diazoamine is formed when dilute or weak acids are used as the solvent. In spite of complete diazotization, however, poor yields of the nitrile were obtained. An insoluble complex containing copper separates upon the addition of the diazonium salt solution to the cuprous cyanide; it is unusually stable to acids and boiling water, a fact which may account for the poor yields of nitrile.

The reaction between the nitrile and methylmagnesium iodide presented certain difficulties. Under a short reaction time and with concentrated reagents a white crystalline solid of m.p. 185–186° was obtained as the chief product; it was unaffected by boiling hydrochloric acid, contained 7.51% nitrogen, and therefore is not analogous to the triphenylpyridine of the type obtained by Ectors (71) in the reaction between benzonitrile and methylmagnesium iodide, a reaction which is favored by high concentration of the reactants. However, when the reagents were diluted and the reaction time lengthened, excellent yields of the methyl ketone were obtained.

It was characterized as the oxime, m.p. 130° [De C. (69), 130°], and as the new 2,4-dinitrophenylhydrazone.

No difficulty was experienced in bromination or in reduction of the bromomethyl ketone. The resulting bromohydrin reacted readily with secondary amines to form the amino alcohols.

EXPERIMENTAL[6]

2,5-Dichlorobenzonitrile (*cf.* 70). A solution of 160 g. (1 mole) of powdered 2,5-dichloroaniline in 40 ml. of 28% hydrochloric acid was rapidly chilled to 0° to precipitate the hydrochloride in finely divided form. A solution of 70 g. (1.02 moles) of sodium nitrite in 200 ml. of water was added over a period of one hour (0–5°) and the temperature was then allowed to rise to 15° where it was held for a half hour. The resulting clear dark brown solution was poured with rapid stirring into a solution of cuprous cyanide covered with two liters of benzene. After stirring the suspension for two hours, the benzene layer was siphoned off, washed with water, dried, and treated with Norit. Evaporation of the benzene under reduced pressure gave 44 g. (25%) (m.p. 129–130°) which was sufficiently pure to use in the next step. It was crystallized from dilute ethanol.

A new preparation of 2,5-dichloroacetophenone. A solution of 13.5 g. (0.074 mole) of 2,5-dichlorobenzonitrile in 500 ml. of absolute ether was added dropwise over 2.5 hours to a refluxing solution of methylmagnesium iodide (prepared from 7.3 g. of magnesium and 70 g. of methyl iodide in 300 ml. of absolute ether). After refluxing for twenty-four hours, the mixture was hydrolyzed with ice and 300 ml. of concentrated hydrochloric acid. The ether extract was separated, washed with water, dried, and evaporated. The residual red oil was vacuum distilled at 3 mm.; b.p. 102–104°; yield 11.7 g. (83.5%).

The *2,4-dinitrophenylhydrazone* (new); m.p. 196–198° after repeated crystallizations from ethyl acetate.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_4O_4$: N, 15.18. Found: N, 14.76.

α-Bromomethyl-2,5-dichlorobenzyl alcohol. The crude oily bromomethyl ketone, prepared according to Procedure 1B, was reduced to the bromohydrin according to Procedure 10. Treatment of the residue with dilute sulfuric acid left an oil which solidified on standing. The yield of light tan solid was 80% (calculated from the methyl ketone); m.p. 92–94°. After three crystallizations from ligroin it melted at 95–96°.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.
Found: C, 36.02; H, 2.75.

XXVIII. THE α-3,5-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

The preparation of 3,5-dichloroacetophenone by the addition of methylmagnesium iodide to 3,5-dichlorobenzaldehyde and oxidation of the resulting carbinol (72), was not feasible because of the unavailability of the starting material. The synthesis of this intermediate was therefore undertaken starting from *p*-aminoacetophenone.

Direct chlorination of *p*-aminoacetophenone was studied extensively in aqueous solution, in benzene, and in carbon tetrachloride. A great deal of resinification occurred and the only identifiable product isolated was *sym.*-trichloroaniline. Finally it was found that by absorbing a calculated weight of chlorine in cold acetic acid, and by adding this solution rapidly to a cold solution of *p*-aminoacetophenone in acetic acid, a 45% yield of 3,5-dichloro-4-aminoacetophenone could be obtained easily and consistently. Coloration was largely avoided by adding an excess of chipped ice to the reaction mixture immediately following the addition of the chlorine solution. The *sym.*-trichloroaniline which was formed as a by-product (29%) was separated by fractional crystallization from ethanol.

Bruining's deamination method (74) involving the refluxing of a mixture of the amine, sulfuric acid, ethanol, and sodium nitrite, gave yields of only 33% when applied to 3,5-dichloro-4-aminoacetophenone, probably because of extreme resistance to diazotization. It was necessary to resort to the diazotization method of Krishna and Bhatia (73), which involves the dropwise addition of a quinoline or pyridine solution of the amine to a solution of sodium nitrite in concentrated hydrochloric acid. Hypophosphorous acid reduction of the diazonium salt solution by the method of Mai (75, 76) proceeded smoothly and gave a yield of 80% of the deamination product. The boiling-ethanol reduction method also gave good yields (70%) but was less convenient because of the large volumes involved.

4-Amino-3-bromo-5-chloroacetophenone was made by bromination of the 4-amino-3-chloroacetophenone for the purpose of preparing 3-bromo-5-chlorophenyl amino alcohols, but the program was abandoned because of the disappointingly low activities of the 3,5-dibromophenyl types.

EXPERIMENTAL[6]

4-Acetylaminoacetophenone (77) was made by the action of acetic anhydride on 4-aminoacetophenone in water suspension. Attempts to chlorinate with calcium hypochlorite (bleach grade "HTH") by adding a 180 ml. solution of 20 g. to a solution of 13.5 g. of acetylaminoacetophenone in a mixture of 25 ml. each of ethanol, water, and concentrated acetic acid, gave a heavy oil which was converted spontaneously in an exothermic reaction into the *4-acetylamino-3-chloroacetophenone*, which solidified and was recrystallized from ethanol; yield 10 g.; m.p. 164° [Chattaway (78), 163°]. The use of an excess of "HTH" gave similar results but only the monochloro compound could be obtained. Other and more drastic conditions for achieving dichlorination failed. Hydrolysis with boiling 4 *N* hydrochloric acid (15% ethanol) (four hours), neutralization of the reaction mixture, extraction with ether, and crystallization from ethanol gave *4-amino-3-chloroacetophenone* in 88% yield; m.p. 91° (C., 92°).

4-Amino-3,5-dichloroacetophenone. A solution of 40 g. of chlorine in 500 ml. of concentrated acetic acid was added rapidly to a solution of 40 g. of 4-aminoacetophenone in 500 ml. of concentrated acetic acid; the temperature throughout was kept at 5°. Immediately following the mixing, the mixture was diluted with 2 l. of ice-water, and the resulting white precipitate was crystallized from 400 ml. of ethanol; 26 g. (44%); m.p. 162–163.5°.

Anal. Calc'd for $C_8H_7Cl_2NO$: N, 6.86. Found: N, 7.02.

From the filtrate upon addition of water was recovered 20 g. (29%) of *sym.*-trichloroaniline.

4-Amino-3-bromo-5-chloroacetophenone was prepared in 82% yield by bromination of the monochloro aminoacetophenone in acetic acid in the presence of sodium acetate (*cf.* 79); recrystallized from 85% ethanol; m.p. 168–169.5°.

Anal. Calc'd for $C_8H_7BrClNO$: C, 38.66; H, 2.84.
Found: C, 38.93; H, 2.93.

3,5-Dichloroacetophenone. A solution of 25 g. of the amine in 180 ml. of pyridine was added slowly to an ice-cold mixture of 18 g. of sodium nitrite in 400 ml. of concentrated hydrochloric acid (below 10°). When the addition was complete, and dilution of a sample with water gave no precipitate, 66 ml. of 50% hypophosphorous acid was added slowly, and stirring was continued for two hours; the temperature throughout was held below 5°. After standing overnight in the ice-box, the mixture was extracted with ether and this extract was washed, dried over sodium sulfate and distilled; the yield of oil was 18.5 g. (80%) of boiling range 107–110° (1 mm.); m.p. 26° [L. and B. (72), 26°].

α-Bromo-3,5-dichloroacetophenone (see Procedure 1). Crude yield (b.p. 135–150°/1 mm.), 96%. B.p. 148°/1 mm. Crystallized from ethanol; short hexagonal prisms; m.p. 73°.

In an identical experiment carried out several years later, the crude oily product after evaporation of the ether and standing in a refrigerator, crystallized in a *lower-melting form* which after repeated crystallizations from petroleum ether melted at 31.5–32.5°. When seeded with the higher-melting form the melting point of the sample rose to 71–72.5°. Attempts to convert this back into the low-melting form were unsuccessful.

An alternative and probably superior preparative procedure utilized conc'd acetic acid as the reaction solvent and precipitation of the product by means of ice; one crystallization from 95% ethanol gave a 68% yield of nearly pure material melting at 70–71.5°.

Anal. Calc'd for $C_8H_5BrCl_2O$: C, 35.86; H, 1.88.
Found: C, 35.89; H, 1.98.

XXIX. α-2,6-DICHLOROPHENYL-β-DI-*n*-OCTYLAMINOETHANOL

2,6-Dichloroacetophenone, made according to Lock and Böck (72), was brominated, and without isolation of the bromomethyl ketone was reduced to the bromohydrin in an over-all yield of 18% from the methyl ketone. The low yield was not surprising in view of the steric effect of the two ortho chlorine atoms.

EXPERIMENTAL[6]

α-Bromomethyl-2,6-dichlorobenzyl alcohol. The crude bromomethyl ketone, prepared according to Procedure 1B, was reduced to the bromohydrin, using Procedure 10Z. The oil obtained after treatment of the residue with dilute sulfuric acid was fractionated at 2 mm. pressure, and the fraction boiling at 135–142° was refractionated twice at 1 mm. The fraction boiling at 136–137° represented a yield of 18% (calculated from the methyl ketone); n_D^{23} 1.5950.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.

Found: C, 35.45; H, 2.59.

α-2,6-Dichlorophenyl-β-di-n-octylaminoethanol hydrochloride (*XXIX*). A solution of 20 g. (0.072 mole) of the bromohydrin and 42 g. (0.173 mole) of dioctylamine in 75 ml. of dry xylene was refluxed for six hours. The mixture was diluted with ether, cooled, and the dioctylamine hydrobromide was filtered; 22.5 g. (93%). The solvent and excess dioctylamine were removed by distillation under 1 mm. pressure. The residual oil was dissolved in dry ether and the hydrochloride was precipitated in four fractions with ethereal hydrogen chloride. The first two fractions melting between 96–100° were combined and crystallized from an ether-ethanol mixture; yield 7 g. (21%); m.p. 98–99.5°.

XXX. THE α-3,5-DIBROMOPHENYL-β-DIALKYLAMINOETHANOLS

A portion of the 3,5-dibromoacetophenone employed here as starting material was obtained by an improvement in the procedure for diazotization and reduction (74) of 4-amino-3,5-dibromoacetophenone (79). Our procedure, using pyridine as the reaction solvent, had one operational advantage in that steam distillation proved to be unnecessary, and the yield was brought to 72%.

The diamylamino ketone appeared to be very unstable, and satisfactory results could not be obtained on reduction; consequently the preparation of this amino alcohol was carried out through the bromohydrin obtained by aluminum isopropoxide reduction of the bromomethyl ketone.

EXPERIMENTAL[6]

Preparation of 3,5-dibromoacetophenone. The method of Krishna and Bhatia (73; *cf.* also 80) was adapted and modified slightly for the diazotization of 4-amino-3,5-dibromoacetophenone. To a well-stirred solution of 20 g. of sodium nitrite in 400 ml. of concentrated hydrochloric acid (cooled to 10°) was added dropwise a solution of 33 g. (0.11 mole) of 4-amino-3,5-dibromoacetophenone in 200 ml. of pyridine. During the addition (requiring about two hours), the reaction temperature was maintained under 10°. The diazonium salt was reduced by the method of Mai (75, 76). The orange colored product melted at 55–58°; 22 g. (72%). After vacuum distillation [b.p. 160–164° (1–2 mm.)] it melted at 60–61°; and after one recrystallization from ethanol, it melted at 64–65° [B. (74), 65°].

α-3,5-Tribromoacetophenone was prepared according to Procedure 1A, using artificial light or gaseous hydrogen bromide to start the reaction. Evaporation of the reaction solvent gave a quantitative yield of almost colorless material; m.p. 78–80°. Recrystallization from ethanol gave colorless needles (67%) of m.p. 84–85°; two additional crystallizations brought the melting point to 85–86°.

Anal. Calc'd for $C_8H_5Br_3O$: C, 26.92; H, 1.41.
Found: C, 26.92; H, 1.52.

α-Bromomethyl-3,5-dibromobenzyl alcohol (*the bromohydrin*). Ninety grams (0.25 mole) of α-3,5-tribromoacetophenone in 300 ml. of dry isopropanol was reduced with 250 ml. of 3 *N* aluminum isopropoxide according to Procedure 10Y. The product solidified upon evaporating the ether solution, and was recrystallized from ethanol (with Darco treatment); 38 g. (53%); m.p. 77–80°. Several additional recrystallizations yielded colorless rods of m.p. 82–83°; a mixture m.p. with the α-bromomethyl ketone (m.p. 85–86°) was 60–68°.

Anal. (91) Calc'd for $C_8H_7Br_3O$: Br, 66.81. Found: Br, 67.23.

α-3,5-Dibromophenyl-β-diethylaminoethanol hydrochloride (*XXXAa*). Twenty-two grams (0.3 mole) of diethylamine was added to a solution of 53.5 g. (0.15 mole) of α-3,5-tribromoacetophenone in dry ether (see Procedure 3L). The amino ketone hydrochloride (hygroscopic) melted at 153–157°. The reduction according to Procedure 6Q gave colorless rods.

α-3,5-Dibromophenyl-β-di-n-amylaminoethanol hydrochloride (*XXXAb*). A mixture of 35.9 g. (0.1 mole) of the crude bromohydrin, 31 g. (0.2 mole) of diamylamine, and 125 ml. of dry xylene was heated under reflux for seven hours (see Procedure 11SQ). The red oil obtained upon concentration of the ether extract was evaporated under reduced pressure onto a cold-finger condenser. A few grams of crystalline material was collected in the first fraction; m.p. 60–65°. This material was not the bromohydrin, as shown by a mixture melting point depression, and it could not have been the ethylene oxide because under the high temperature it would not have escaped reaction. Doubtless it is the 3,5-dibromoacetophenone (m.p. 65°) resulting from hydramine fission, but a mixture melting point identification was not made. The other fractions (15 g. of yellowish oil) were dissolved in dry ether; addition of ethereal hydrogen chloride precipitated 15 g. of crystalline hydrochloride.

Pyrolysis (bath temperature 300–312°) of the hydrochloride produced the secondary amine hydrochloride in excellent yield. However, attempts to isolate the other fragment of hydramine fission, 3,5-dibromoacetophenone, failed.

α-3,5-Dibromophenyl-β-benzylmethylaminoethanol (*XXXAc*). Reduction of 36 g. (0.083 mole) of the amino ketone hydrochloride with 300 ml. of 1 *N* aluminum isopropoxide was performed according to Procedure 6SR. Attempts to form a crystalline hydrochloride failed. The product was first evaporated under reduced pressure onto a cold-finger condenser and then fractionated at a pressure of 2 mm. under a stream of nitrogen, using a heated 8-inch Vigreux column.

XXXI. α-2,4-DIISOPROPYLPHENYL-β-DIETHYLAMINOETHANOL

2,4-Diisopropylacetophenone. An equimolar mixture of acetyl chloride and 1,3-diisopropylbenzene was introduced dropwise into a cooled mixture of 1.4 moles of anhydrous aluminum chloride and carbon disulfide over a period of eight hours. After removing the solvent under reduced pressure, the residue was poured onto cracked ice and extracted with ether. The colorless product distilled at 93–96° (1–2 mm.); n_D^{24} 1.5108–1.5113. The yields in two runs were 81 and 87% respectively. The orientation in the Friedel-Crafts reaction here was assumed.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.30; H, 9.87.
Found: C, 83.01; H, 10.20.

XXXII. THE α-CARVACRYL-β-DIALKYLAMINOETHANOLS

All except one of the compounds in this series were prepared by the usual scheme starting from 2-acetyl-*p*-cymene. One tertiary alcohol, namely, α-carvacryl-α-*n*-propyl-β-diethylaminoethanol, was prepared from the diethylamino ketone by reaction with *n*-propylmagnesium bromide.

EXPERIMENTAL[6]

The *dibutylamino* compound (XXXIIAb) distilled at 171–175° under 4 mm. The hydrochloride was formed by dissolving the free base in acetone, acidifying with ethereal hydrogen chloride and diluting with ether.

β-Piperidyl- and β-morpholinyl-α-carvacrylethanol hydrochlorides (*XXXIIAc, d*). The amino ketones (free bases) were liberated from the hydrochlorides with sodium hydroxide, and the resulting oils (isolated from the ether extracts) were reduced according to Procedure 5Q. The products were precipitated from acetone by acidification with ethereal hydrogen chloride.

α-Carvacryl-α-n-propyl-β-diethylaminoethanol (*XXXIIAe*). A solution of α-diethylamino-5-isopropyl-2-methylacetophenone was prepared from 0.5 mole of the bromomethyl ketone by overnight treatment at room temperature with an excess of diethylamine in ether. The diethylamine hydrobromide was filtered, the filtrate was washed with saturated sodium chloride, and the ethereal solution was dried. This dried solution was added to 145 ml. of 2.5 *N* *n*-propylmagnesium bromide rapidly enough to maintain gentle refluxing. The mixture was stirred for two hours and then hydrolyzed with 130 ml. of 6 *N* hydrochloric acid and ice. The aqueous layer was made alkaline and repeatedly extracted with ether. The ether extract was dried over sodium sulfate and the ether was evaporated. The residue was fractionally distilled several times under a pressure of 5 mm.

XXXIII. THE α-(2,4-DICHLORO-3-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

In this series 2,6-dichlorotoluene was employed as starting material. A Friedel-Crafts reaction using acetyl chloride yielded 2,4-dichloro-3-methylacetophenone. The structure of this was proved by oxidation to a dichloroisophthalic acid (2, 4), which upon catalytic-reductive dehalogenation with palladium-black yielded isophthalic acid.

The 2,4-dichloro-3-methylacetophenone was brominated in ether, and aluminum isopropoxide reduction produced α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol, which in turn was condensed with secondary amines to give the desired amino alcohols.

EXPERIMENTAL[6]

2,4-Dichloro-3-methylacetophenone. A stirred mixture of 346 g. of 2,6-dichlorotoluene and 280 g. of powdered anhydrous aluminum chloride was heated on a boiling water-bath, and 162 g. of acetyl chloride was added slowly. Heating was continued for 2.5 hours, and the complex was then hydrolyzed by pouring over an ice-hydrochloric acid mixture. The resulting pasty solid was filtered, dried, and purified by distillation *in vacuo*; b.p. 147–148° (10 mm.); m.p. 38°; yield 195 g. (45%).

Anal. Calc'd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97.

Found: C, 53.48; H, 3.87.

Proof of structure. A mixture of 5 g. of the above acetophenone derivative, 200 ml. of water, 20 g. of potassium permanganate, and 5 ml. of 50% sodium hydroxide was heated under reflux for three hours, after which time 25 ml. of water was distilled off in order to remove any remaining starting material. After the reaction mixture had cooled, the manganese dioxide was filtered off, and the filtrate was acidified with hydrochloric acid and evaporated to dryness. The resulting crude dichloroisophthalic acid (2,4) was reductively dehalogenated by palladium-Darco hydrogenation in dilute acid solution; needles; m.p. 344°; a mixture melting point with isophthalic acid showed no depression.

2,4-Dichloro-3-methylphenacyl bromide. This compound was prepared according to Procedure IA. Forty-two grams of bromine was added slowly to a stirred solution of 53 g. of 2,4-dichloro-3-methylacetophenone in 150 ml. of dry ether. The ether was then distilled off and the remaining oil distilled under reduced pressure. The material exhibited a tendency to remain as a supercooled liquid after distillation; b.p. 167–169° (8 mm.); m.p. 61°; yield 60 g. (82%).

Anal. Calc'd for $C_9H_7BrCl_2O$: C, 38.33; H, 2.51.
Found: C, 38.08; H, 2.52.

α-Bromomethyl-2,4-dichloro-3-methylbenzyl alcohol. The preparation of this compound was essentially the same as given in Procedure 10, using 60 g. of 2,4-dichloro-3-methylphenacyl bromide and 400 ml. of 1.5 *N* aluminum isopropoxide. Reduction was complete in ten hours. After evaporation of the excess isopropanol under reduced pressure the reaction mixture was hydrolyzed with 6 *N* sulfuric acid. The resulting solid was filtered, washed with water, dried, and recrystallized from petroleum ether; m.p. 114°; yield 50 g. (83%).

Anal. Calc'd for $C_9H_9BrCl_2O$: C, 38.06; H, 3.19.
Found: C, 38.05; H, 3.22.

α-(2,4-Dichloro-3-methylphenyl)-β-di-n-butylaminoethanol (XXXIIIa). A solution of 50 g. of 2,4-dichloro-3-methylphenacyl bromide in 200 ml. of dry ether was added slowly to an ice-cold solution of 48 g. of dibutylamine in 200 ml. of dry ether (Procedure 3M). After the addition, the solution was stirred for four hours at room temperature, the dibutylamine hydrobromide was filtered off, and the ether evaporated *in vacuo* under nitrogen at room temperature. The oil was converted into a hydrochloride, which was then reduced without purification, according to Procedure 7R, using 450 ml. of 1.1 *N* aluminum isopropoxide. After reducing for five hours, the excess isopropanol was evaporated under reduced pressure, and the remaining oil hydrolyzed with 50% sodium hydroxide.

After extracting into ether and drying, the oil was distilled *in vacuo* under nitrogen.

α-(2,4-Dichloro-3-methylphenyl)-β-di-n-amylaminoethanol (XXXIIIb). (Procedure 11R). A mixture of 40 g. of α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol, 45 g. of dibutylamine, and 150 ml. of dry xylene was refluxed for twelve hours and cooled. Ether was added and the dibutylamine hydrobromide filtered. The filtrate was washed with 10% sodium hydroxide, then with water, and was dried over sodium sulfate. After evaporating the solvent an oil remained, which was fractionally distilled *in vacuo* under nitrogen.

α-(2,4-Dichloro-3-methylphenyl)-β-di-n-octylaminoethanol hydrochloride (XXXIIIc). Following Procedure 11RQ, 50 g. of α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol and 125 g. of dioctylamine were used with no added solvent. After heating at 130° for four hours, the mixture was cooled, diluted with ether, and the dioctylamine hydrobromide filtered. The filtrate was washed once with 30% sodium hydroxide and twice with water. After drying the solution over sodium sulfate, the ether was evaporated, and the remaining oil distilled *in vacuo* under nitrogen. The base was converted into the hydrochloride in a mixture of ether and petroleum ether, and this was recrystallized from ethyl acetate.

α-(2,4-Dichloro-3-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (XXXIIId). Procedure 11RQ was followed using 50 g. of α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol, 43 g. of benzylmethylamine and 150 ml. of dry benzene. The reaction mixture was heated under reflux for eight hours, and the product was isolated according to the procedure given for XXXIIIc.

XXXIV. THE α-(4,5-DICHLORO-2-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

The starting material for this series was 3,4-dichlorotoluene. The Friedel-Crafts reaction with acetyl chloride gave 4,5-dichloro-2-methylacetophenone, the structure of which was shown (a) by oxidation to the known 4,5-dichlorophthalic acid (81), and (as further confirmation) (b) by catalytic reduction of this to phthalic acid.

The 4,5-dichloro-2-methylacetophenone was converted by bromination in ether to the α-bromomethyl ketone, which was then reduced by aluminum isopropoxide to α-bromomethyl-4,5-dichloro-2-methylbenzyl alcohol. The desired amino alcohols were obtained by subsequent condensations with the appropriate secondary amines.

EXPERIMENTAL[6]

4,5-Dichloro-2-methylacetophenone. To a stirred solution of 320 g. of 3,4-dichlorotoluene and 260 g. of powdered anhydrous aluminum chloride (heated on a boiling water bath) was added slowly 150 g. of acetyl chloride. After heating for an additional three hours, the material was hydrolyzed by pouring into an ice-hydrochloric acid mixture. The resulting waxy solid was filtered, dried, and distilled under reduced pressure; b.p. 125–127° (2 mm.); m.p. 55° (after two recrystallizations from ethanol); yield 243 g. (60%).

Anal. Calc'd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97.
Found: C, 53.10; H, 4.04.

The proof of structure was carried out as in the case of 2,4-dichloro-3-methylacetophenone (see Section XXXIII) by oxidation to the known 4,5-dichlorophthalic acid; m.p. 202° [V. (79), about 200° under rapid heating]. Catalytic reductive dehalogenation gave phthalic acid.

4,5-Dichloro-2-methylphenacyl bromide was made essentially by Procedure 1A, using 240 g. of 4,5-dichloro-2-methylacetophenone dissolved in 900 ml. of dry ether, with slow addition of 191 g. of dry bromine. The ether was distilled off, and the residual oil was distilled under reduced pressure; yield 284 g. (85%); b.p. 156° (2 mm.). Two recrystallizations from ethanol gave a sample melting at 73–74°.

Anal. Calc'd for $C_9H_7BrCl_2O$: C, 38.33; H, 2.51.
Found: C, 38.06; H, 2.39.

α-Bromomethyl-4,5-dichloro-2-methylbenzyl alcohol (the bromohydrin). Procedure 10Y was employed, using 76 g. of 4,5-dichloro-2-methylphenacyl bromide and 680 ml. of 1.24 *N* aluminum isopropoxide. Reduction was complete in seven hours, after which the excess isopropanol was evaporated under reduced pressure and the residual material hydrolyzed with 6 *N* sulfuric acid. The solid was filtered, washed with water, dried, and recrystallized from petroleum ether; yield 47.5 g. (62%). Three recrystallizations gave a sample melting at 103°.

Anal. Calc'd for $C_9H_9BrCl_2O$: C, 38.06; H, 3.19.
Found: C, 38.42; H, 3.14.

The *amino alcohols* were prepared according to the procedures indicated in Table I. The vacuum fractionations were carried out under an atmosphere of nitrogen. In the case of the *dioctylamino alcohol*, a crystalline hydrochloride could be obtained by neutralizing an ethyl acetate solution of the pure base with ethereal hydrogen chloride, heating to boiling, and allowing to cool slowly.

XXXV. THE α-4-CHLOROPHENYL-β-ALKYL-β-DIALKYLAMINOETHANOLS

In this series the amino alcohols were prepared with three different β-alkyl groups, methyl, ethyl, and *n*-butyl. 4-Chloropropiophenone (commercially available), 4-chlorobutyrophenone, and 4-chlorocaprophenone, respectively, were chosen as starting materials.

The α-bromo ketones were made and used directly, without isolation, in ether solution. A small sample of α-bromo-4-chloropropiophenone (one of the strongest lachrymators encountered in this work) was isolated, and shown to be identical in its properties with the compound obtained by Collet (17) in the Friedel-Crafts reaction between chlorobenzene and α-bromopropionyl chloride.

Evidence for the displacement of nuclear halogen was obtained during the distillation of two amino alcohols (XXXVAa and b); in this operation there were produced and isolated significant quantities of the secondary amine hydrochlorides (*cf.* Section III).

EXPERIMENTAL[6]

4-Chlorobutyrophenone was prepared according to Morgan and Hickinbottom (82) in 78% yield.

4-Chlorocaprophenone. A well-stirred mixture of 225 g. (2 moles) of chlorobenzene, 600 g. of carbon disulfide, and 250 g. (1.87 moles) of anhydrous aluminum chloride, was heated on a steam-bath until refluxing started, and 300 g. (2.2 moles) of caproyl chloride was added slowly over a period of one hour. Refluxing was continued for an additional hour. The solvent was distilled off, and the cooled residue was hydrolyzed in ice and hydrochloric acid. The resulting solid was recrystallized from ethanol; 270 g. (65%); m.p. 61.5–62.5°. The orientation here was assumed.

Anal. Calc'd for $C_{12}H_{15}ClNO$: C, 68.40; H, 7.18.
Found: C, 68.14; H, 7.14.

Preparation of α-bromo-4-chloropropiophenone. 4-Chloropropiophenone was brominated according to Procedure 2. The solvent was evaporated from a small portion, and recrystallization of the crude material from ethanol (with Darco treatment) gave colorless cubes of m.p. 78–79° [C. (17), 77.5°].

XXXVI. THE α-4-BROMOPHENYL-β-METHYL-β-DI-*n*-ALKYLAMINOETHANOLS

EXPERIMENTAL[6]

Preparation of 4-bromopropiophenone was carried out according to the procedure given for the preparation of 4-chlorocaprophenone (see Section XXXV) (*cf.* 83, 84). A 38% yield was obtained; m.p. 45–46° [E. and L. (84), 47°].

α-4-Dibromopropiophenone was prepared according to Procedure 1A; yield 65%; m.p. 84–84.5° (not analyzed).

XXXVII. α-(4-BROMO-3-METHYLPHENYL)-β-METHYL-β-BENZYLMETHYLAMINOETHANOL

4-Bromo-3-methylpropiophenone employed as the starting material, was obtained by the Friedel-Crafts reaction between propionyl chloride and 2-bromotoluene. The orientation is assumed here and is based on analogy to the acetylation of 2-bromotoluene (see Section XXII). It is doubtful however, that the products obtained here are entirely free from the structural isomer.

EXPERIMENTAL[6]

4-Bromo-3-methylpropiophenone. Two moles of propionyl chloride was added slowly under mechanical stirring and gentle refluxing, to a mixture of two moles of 2-bromotoluene, 2 moles of anhydrous aluminum chloride, and 800 ml. of carbon disulfide. The product was worked up according to the usual procedure (54), and vacuum distillation gave 170 g. (38%); colorless oil; b.p. 109–110° (1–2 mm.); n_D^{20} 1.5611 (not analyzed).

An ethereal solution of *α-4-dibromo-3-methylpropiophenone* was prepared according to Procedure 2.

α-(4-Bromo-3-methylphenyl)-β-methyl-β-benzylmethylaminoethanol (*XXXVII*). To the aliquot portion (0.2 mole) of the α-bromomethyl ketone was added 84.4 g. (0.4 mole) of benzylmethylamine; the reaction mixture was worked up according to Procedure 3L. The resulting amino ketone hydrochloride (27 g. of m.p. 172–175°) was reduced according to Procedure 6U, and the amino alcohol crystallized from ethanol as colorless rectangular rods.

XXXVIII. SOME ARYL AMINO KETONES AND AMINO ALCOHOLS CARRYING THE CAPRYL CHAIN

A few representative amino alcohols and amino ketones were made from caprophenone and the para-ethyl, para-isopropyl and para-*tert.*-butyl homologs. The last three ketones were made by the Friedel-Crafts reaction between caproyl chloride and ethyl-, isopropyl- and *tert.*-butylbenzenes, respectively. The amino alcohols in these series may exist in stereoisomeric forms. The few compounds obtained as oils doubtless were mixtures. In the case of those obtained as crystalline hydrochlorides, the compounds prepared for test appeared to be homogeneous, but no attempt was made to obtain the pure stereoisomers.

EXPERIMENTAL[6]

β-(Di-n-butylamino)-α-phenylhexanol (*XXXVIIIAa*). The α-bromocaprophenone was prepared from caprophenone according to Procedure 2 and treated with dibutylamine in ether (thirty hours), the reaction proceeding very slowly (incomplete). The crude amino ketone was obtained as an oily residue and was reduced by Procedure 5; the product distilled under 4 mm. at 185–186°; redistillation gave cuts of n_D^{20} 1.4918–1.4920; 11 g. (16%).

α-(N-Piperidyl)caprophenone hydrochloride (*XXXVIIIBa*) was prepared like the α-morpholinylcaprophenone hydrochloride (below), and was recrystallized twice from acetone.

α-(N-Morpholinyl)caprophenone hydrochloride (*XXXVIIIBb*). Reaction between an aliquot portion of the ether solution of α-bromocaprophenone (Procedure 2) and an excess of morpholine (twenty-four hours at room temperature) gave an oil which was converted into a crystalline hydrochloride from acetone by the addition of ethereal hydrogen chloride (yield calculated from caprophenone was 84%); m.p. 188–190°. It was crystallized twice from acetone.

β-(N-Morpholinyl)-α-phenylhexanol hydrochloride (*XXXVIIIAc*) was prepared by reduction of the amino ketone (Procedure 5), and the oil obtained crystallized from acetone upon addition of ethereal hydrogen chloride. The product showed a marked mixture melting point depression with the amino ketone hydrochloride. The yield was 16 g.; m.p. 207–210°; it was recrystallized three times by solution in hot methanol, and addition of dry ether and cooling; m.p. 215–217°.

A second crop of crystals was obtained from the mother liquors of the first crystallization (35 g.; m.p. 140–142°); presumably this is either the stereoisomer or a mixture of stereoisomers; it was recrystallized once from methanol by addition of dry ether; m.p. 140°.

Anal. Calc'd for $C_{16}H_{25}NO_2 \cdot HCl$: C, 64.09; H, 8.74.
Found: C, 63.81; H, 9.00.

4-Ethylcaprophenone was prepared exactly according to the procedure described for the 4-*tert.*-butyl analog. The product distilling at 150–155° (8–10 mm.) was 222 g. (83%). Redistillation gave a cut of n_D^{24} 1.5103. The orientation was assumed.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.30; H, 9.87.
Found: C, 82.08; H, 10.04.

β-(Di-n-butylamino)-α-(4-ethylphenyl)hexanol (*XXXVIIIAd*) was prepared through α-bromo-4-ethylcaprophenone (not isolated) and aluminum isopropoxide reduction of the crude amino ketone by a procedure identical with that described for the 4-*tert.*-butyl analog (Procedures 3K and 5TR). The product was fractionally distilled at 1–2 mm.; yield 12.7 g. (19%), from which cuts of b.p. 140–150° were taken for analysis and test; n_D^{25} 1.4830–1.4836. Doubtless this was a mixture of stereoisomers.

4-Isopropylcaprophenone was made in the same way as 4-*tert.*-butylcaprophenone (see below). However, here the reaction temperature was maintained at 10° during the addition, and then the reaction mixture was stirred at room temperature for four hours. The yield was 87%; b.p. 168–176° (12–13 mm.). The orientation was assumed (not analyzed).

The *oxime* crystallized from dilute ethanol as colorless needles of m.p. 54–55°.

Anal. Calc'd for $C_{15}H_{23}NO$: N, 6.01. Found: N, 6.11.

4-tert.-Butylcaprophenone was prepared by dropwise addition over eight hours of 105 g. (0.81 mole) of *tert.*-butylbenzene and 108 g. (0.81 mole) of caproyl chloride with stirring into a mixture of 106 g. (0.8 mole) of anhydrous aluminum chloride and 150 ml. of carbon disulfide maintained at 23°. The mixture was heated to reflux, allowed to stand for twelve hours, and hydrolyzed in ice and hydrochloric acid. Fractional distillation gave a nearly pure material; 134 g. (71%); redistillation gave a cut of b.p. 120–130°; n_D^{25} 1.5065.

Anal. Calc'd for $C_{16}H_{24}O$: C, 82.70; H, 10.41.
Found: C, 82.65; H, 10.67.

α-(4-tert.-Butylphenyl)-β-(diethylamino)hexanol hydrochloride (XXXVIIIAf). A solution of 47 g. (0.2 mole) of 4-*tert.*-butylcaprophenone in 300 ml. of ether was allowed to react with 32 g. (0.2 mole) of bromine, added slowly with preliminary heating to initiate reaction. The solution was washed, dried over sodium sulfate, and treated with 29.2 g. (0.4 mole) of diethylamine at room temperature (six days). The red solution was filtered from diethylamine hydrobromide (97% yield) and evaporated. The resulting red oil was reduced by aluminum isopropoxide according to Procedure 5R; three cuts were taken of n_D^{25} 1.4963, 1.4959, and 1.4960 (15.5 g.; 24%). It was converted into the hydrochloride from ether, and crystallized three times from ethyl acetate.

XXXIX. SOME AMINO KETONES AND ALCOHOLS MADE FROM LAUROPHENONE

It seemed of interest to prepare some representative compounds in this series where the low nuclear molecular weight (of the phenyl group) was partly compensated by a long carbon chain, carrying the amino alcohol group in the proper location next to the aryl group. These compounds were of interest also for comparison with the completely aliphatic amino alcohols made from lauric acid (85).

Laurophenone was brominated in carbon tetrachloride. The α-bromo ketone in ether reacted slowly with the secondary amines, diethylamine, piperidine, and morpholine, but only the amino ketones from the latter two amines were obtained as crystalline hydrochlorides.

Reduction of the amino ketones was found to be accomplished best by the aluminum isopropoxide method, but mixtures of stereoisomers invariably resulted. One stereoisomer was usually obtainable in a pure state by fractional recrystallizations, and the tests were carried out only on what appeared to be homogeneous samples. Because of the lack of time little effort was made to obtain the more difficultly isolable stereoisomers for comparison. It is noteworthy that in one case, namely α-piperidyllaurophenone, reduction by sodium and alcohol was successful and gave as the chief product the same compound as was obtained in the aluminum isopropoxide reduction.

Laurophenone was used in a typical Mannich reaction which proceeded satisfactorily but very slowly, and the β-dimethylamino ketone (XXXIXD) was obtained in 43% yield. Since the diethylamino analog was considered to be a better choice for screening tests, an attempt was made to make the corresponding amino ketone and to reduce this to the amino alcohol. However, the amino ketone was not easily obtained and it was not isolated in crystalline form; it was used in the crude condition, however, and was reduced with aluminum isopropoxide to the amino alcohol (XXXIXB), which was obtained in very small yield as a crystalline hydrochloride. Only the one form was isolated although a stereoisomer is of course possible.

EXPERIMENTAL[6]

α-Bromolaurophenone. Laurophenone (32 g.) in 150 ml. of carbon tetrachloride was treated dropwise with 21 g. of bromine in 50 ml. of the same solvent; evaporation gave an oil which crystallized; it was recrystallized from ethanol; 32 g. (78%); m.p. 29–30°.

Anal. Calc'd for $C_{18}H_{27}BrO$: C, 63.71; H, 8.02.

Found: C, 63.88; H, 8.30.

2-Diethylamino-1-phenyldodecanol-1 hydrochloride (XXXIXAa). Numerous variations in the condensation between diethylamine and α-bromolaurophenone failed to yield a crystalline hydrochloride of the amino ketone. The best results were obtained in the cold but the reaction was very slow and incomplete under the conditions finally chosen. A reaction mixture of 18 g. of α-bromolaurophenone and 50 ml. of diethylamine was allowed to stand in the refrigerator for one week and was filtered from diethylamine hydrobromide. Dilution with ether and treatment with 10% hydrochloric acid gave three layers. The lower two layers were drawn off and made alkaline with sodium carbonate, and the liberated base was extracted by ether, from which 16 g. of oil was obtained. Repeated attempts to crystallize the compound as the base or as a salt failed, and it was reduced in this crude form. A solution of 37 g. of the crude amino ketone in 300 ml. of 3 *N* aluminum isopropoxide was refluxed for four hours, when the distillate failed to give an acetone test. The product, isolated in the usual way (Procedure 5) and extracted into ether, was isolated as an oil. It was dissolved in acetone and precipitated as a crystalline hydrochloride with ethereal hydrogen chloride; yield 17 g. of m.p. 70–74°; it was recrystallized five times by dissolving in hot acetone and adding dry ether; m.p. 81–83°.

Catalytic reduction of the amino ketone in methanol using platinum oxide proceeded readily, and did not stop after absorption of one molecule of hydrogen. The reaction was interrupted, and on working up the products a very small amount of crystalline hydrochloride was isolated (m.p. 134–135°). Presumably this was a stereoisomer of the product of aluminum isopropoxide reduction, but it was not investigated further.

α-(N-Piperidyl)laurophenone hydrochloride (XXXIXCa). A solution of 20 g. of α-bromolaurophenone in 50 ml. of piperidine, after standing overnight, was filtered from piperidine hydrobromide, diluted with ether, washed with water and dried. Evaporation gave an oil which formed a crystalline hydrochloride from acetone upon addition of ethereal hydrogen chloride; 15 g. (67%); m.p. 119–121°. It was recrystallized four times by dissolving in hot acetone and adding dry ether.

1-Phenyl-2-(N-piperidyl)dodecanol-1 hydrochloride (XXXIXAb). Reduction of 45 g. of the crude amino ketone (base) by 500 ml. of 1.5 *N* aluminum isopropoxide in the usual way (four hours; *cf.* Procedure 5), gave an oil which was converted from acetone into a crystalline hydrochloride (7 g. of m.p. 165–173°); a second crop melting at 95–105° (26 g.) evidently was a mixture of stereoisomers. The first precipitate was repeatedly crystallized from acetone; m.p. 183–187°. The second precipitate, on repeated crystallizations, yielded a considerable amount of additional product of m.p. 183–184°.

Reduction of 4.3 g. of the amino ketone hydrochloride in 350 ml. of absolute ethanol by 15 g. of metallic sodium added over three hours, gave a basic oil which gave a precipitate from acetone upon addition of ethereal hydrogen chloride; 1 g. (23%); m.p. 172–174°. It was purified and shown to be identical with the chief product of the aluminum isopropoxide reduction (m.p. 183–184°).

α-(N-Morpholinyl)laurophenone hydrochloride (*XXXIXCb*) was prepared exactly as was the piperidyl compound. It was recrystallized three times from acetone; m.p. 162–165°.

2-(N-Morpholinyl)-1-phenyldodecanol-1 hydrochloride (*XXXIXAc*) was obtained by aluminum isopropoxide reduction of 50 g. of the crude amino ketone (base) in the same way as the piperidyl analog. The amino alcohol hydrochloride was obtained as two crops, 12 g. of m.p. 167–174° and 29 g. of m.p. 102–105°. The second crop, presumably a mixture of stereoisomers, was not investigated. The first crop was repeatedly crystallized from acetone; m.p. 178–180°.

α-(Dimethylaminomethyl)laurophenone hydrochloride (*XXXIXD*). A suspension of 4.5 g. of dimethylamine hydrochloride, 13 g. of laurophenone and 4.5 g. of paraformaldehyde in 50 ml. of absolute ethanol, acidified with four drops of ethanolic hydrogen chloride, was refluxed for nine days (the reaction had been found in preliminary runs to be exceedingly slow). The mixture was treated with excess ether and hydrochloric acid and the ether layer was evaporated, giving 7.5 g. (43%) of a crystalline hydrochloride of m.p. 107–119°. A small amount of the same compound crystallized from the aqueous layer (0.1 g.). Repeated crystallizations from acetone by addition of dry ether gave a pure product of m.p. 129–129.5°.

2-(Diethylaminomethyl)-1-phenyldodecanol-1 hydrochloride (*XXXIXB*). Many experiments were carried out before the desired amount of ketone could be obtained in significant yield; it could not be obtained as a crystalline hydrochloride under the usual conditions and was consequently reduced without purification.

A solution of 52 g. of laurophenone, 30 g. of diethylamine hydrochloride, and 20 g. of paraformaldehyde in 200 ml. of absolute ethanol and 4 ml. of concentrated ethanolic hydrogen chloride was refluxed for ten days with addition, at intervals, of a total of 34 g. of additional paraformaldehyde. Evaporation of the ethanol and treatment with dilute hydrochloric acid and ether produced three layers, the middle layer consisting of the oily amino ketone hydrochloride. From the ether layer 13 g. of laurophenone was recovered. Treatment of the two lower layers with sodium carbonate and extraction with ether gave 41 g. of crude amino ketone.

A solution of 7 g. of the crude amino ketone in 300 ml. of 0.75 *N* aluminum isopropoxide was refluxed for six hours, when acetone could no longer be detected in the distillate. The product was isolated as an oil which was converted in the usual way into a hydrochloride (from acetone with ethereal hydrogen chloride); yield 1 g. (8% calculated from laurophenone); m.p. after two crystallizations from acetone, 154–155°. It was soluble in water.

XXXX. 3-BROMO-4-CHLOROACETOPHENONE AND 3-IODO-4-CHLOROACETOPHENONE

The preparation of the 3-bromo-4-chloro and 3-iodo-4-chloro series of dialkylaminoethanols was begun but was discontinued in favor of more pressing problems.

4-Chloroacetophenone was chosen as starting material, and was nitrated, reduced, diazotized, and then converted into the 3-bromo-4-chloro-and 3-iodo-4-chloro-acetophenones by treatment with cuprous bromide and potassium iodide, respectively. The structures of these two new acetophenones were verified by oxidation to the known dihalogenobenzoic acids.

EXPERIMENTAL[6]

4-Chloro-3-nitroacetophenone (86, 87) was best obtained using mixed nitric and sulfuric acids (87) at a temperature of −5°, and the detailed procedure of Morgan and Watson (88) for the nitration of acetophenone itself; white crystals; yield after recrystallizing from dilute acetic acid, 83%; m.p. 97–99° [Le F. and Le F. (86), 99–101°] [M., S., and S. (87), yellow crystals, 77%, 104°].

A lower nitration temperature than −5° gave only a partial conversion of starting material into the nitro compound (29% at −30°, and 38% at −15°). The use of a less drastic nitrating mixture (nitric acid alone at 5° or a sulfuric acid solution of sodium nitrate at 15°) resulted only in the recovery of starting material. When more drastic conditions were tried, little or none of the desired product was obtained; carrying out the nitration at 10° gave only a 5% yield; the use of nitric acid at room temperature or a sulfuric acid solution of sodium nitrate at 40° gave products (m.p. 114–117° and oil, respectively) which were not investigated further.

3-Amino-4-chloroacetophenone was prepared by adding 10 g. of 4-chloro-3-nitroacetophenone to 45 ml. of concentrated hydrochloric acid containing 34 g. of stannous chloride dihydrate; the hydrochloride precipitated and was converted to the free base by alkali; colorless crystals, m.p. 105–107°; yield 7 g. (82%).

Anal. Calc'd for C_8H_8ClNO: N, 8.26. Found: N, 8.11.

3-Bromo-4-chloroacetophenone was prepared by suspending 5.1 g. (0.03 mole) of 3-amino-4-chloroacetophenone in a mixture of 25 ml. of 40% hydrobromic acid and 10 ml. of water under mechanical stirring, cooling in an ice-salt bath, slowly adding an excess of sodium nitrite solution, destroying the excess a few minutes later with urea, allowing the mixture to stir for another hour, and then pouring it into a warm solution which consisted of 0.03 mole of freshly prepared cuprous bromide dissolved in 40% hydrobromic acid. The product was filtered and recrystallized from 50% ethanol; light orange solid; m.p. 80–82°; yield 4.8 g. (68%). A pure sample was obtained by vacuum sublimation, white crystals, m.p. 85.5°.

Anal. Calc'd for C_8H_6BrClO: C, 41.15; H, 2.59.
Found: C, 41.39; H, 2.73.

Oxidation with alkaline permanganate gave *3-bromo-4-chlorobenzoic acid* in 70% yield, m.p. 217–219° [H. & B. (89), 215–216°].

4-Chloro-3-iodoacetophenone was prepared by adding 50 g. of 4-chloro-3-nitroacetophenone to 225 ml. of concentrated hydrochloric acid containing 170 g. of stannous chloride dihydrate, diluting with 500 ml. of glacial acetic acid (after the reaction subsided), cooling to −1° in an ice-salt bath, adding 46.5 g. (0.67 mole) of sodium nitrite in 70 ml. of water over a period of two and one-half hours, stirring for an additional two hours, adding 40 g. (0.67 mole) of urea in 100 ml. of water during one hour, adding 41 g. (0.25 mole) of potassium iodide in 200 ml. of water, allowing the cooled mixture to stir overnight, warming it on a water-bath for thirty minutes, diluting with water, again cooling, filtering, and recrystallizing from 95% ethanol; the yield was 18 g. (26%); light orange crystals; m.p. 84–86°.

Anal. Calc'd for C_8H_6ClIO: C, 34.25; H, 2.16.
Found: C, 34.39; H, 2.30.

Oxidation with alkaline permanganate gave *4-chloro-3-iodobenzoic acid* in almost quantitative yield; m.p. 217–219° [H. & B. (89), 216–217°].

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TABLE II. ANALYSES

COMPOUND NO.	EMPIRICAL FORMULA	C (or N or Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
IA a	$C_{24}H_{43}NO$	$^{N}3.87$	4.15	—	—
b	$C_{26}H_{47}NO$	$^{N}3.59$	3.79	—	—
c	$C_{16}H_{19}NO$	$^{N}5.81$	6.04	—	—
d	$C_{16}H_{18}ClNO$	$^{N}5.11$	4.99	—	—
e	$C_{16}H_{18}ClNO$	$^{N}5.11$	5.40	—	—
f	$C_{22}H_{23}NO\cdot HCl$	74.66	74.60	6.84	6.81[a]
IIA a	$C_{12}H_{18}ClNO$	$^{N}6.15$	6.03	—	—
b	$C_{16}H_{26}ClNO$	$^{N}4.94$	4.79	—	—
b_1	$C_{16}H_{26}ClNO\cdot HCl$	59.99	59.82	8.50	8.32
c	$C_{16}H_{26}ClNO$	67.70	67.34	9.23	9.38
d	$C_{18}H_{30}ClNO$	69.32	69.39	9.70	9.68[a]
e	$C_{18}H_{30}ClNO$	$^{N}4.49$	4.49	—	—
f	$C_{20}H_{34}ClNO$	70.66	70.55	10.08	10.38
g	$C_{22}H_{38}ClNO\cdot HCl$	$^{N}3.46$	3.57	—	—
h	$C_{24}H_{42}ClNO$	72.78	72.43	10.69	10.85
h_1	$C_{24}H_{42}ClNO\cdot HCl$	$^{Cl^-}8.20$	8.29	—	—
i	$C_{24}H_{42}ClNO$	72.78	72.43	10.69	10.93[a]
j	$C_{26}H_{46}ClNO$	73.63	73.96	10.93	11.28
k	$C_{28}H_{50}ClNO$	74.37	74.73	11.15	11.48[a]
l	$C_{30}H_{54}ClNO$	$^{N}2.92$	3.23	—	—
l_1	$C_{30}H_{54}ClNO\cdot HCl$	$^{Cl^-}6.86$	6.69	—	—
m	$C_{32}H_{58}ClNO$	$^{N}2.76$	2.90	—	—
n	$C_{34}H_{62}ClNO$	$^{N}2.61$	2.85	—	—
o	$C_{16}H_{18}ClNO\cdot HCl$	$^{Cl^-}11.36$	11.73	—	—
p	$C_{17}H_{20}ClNO$	$^{N}4.83$	4.66	—	—
q	$C_{18}H_{22}ClNO$	71.15	71.23	7.30	7.14
r	$C_{18}H_{22}ClNO$	$^{N}4.61$	4.85	—	—
r_1	$C_{18}H_{22}ClNO\cdot HCl$	63.53	63.46	6.81	6.80
s	$C_{19}H_{24}ClNO$	71.79	71.61	7.61	7.44
t	$C_{19}H_{24}ClNO\cdot HCl$	64.40	64.82	7.11	6.85[a]
u	$C_{20}H_{26}ClNO$	$^{N}4.22$	4.42	—	—
v	$C_{27}H_{40}ClNO$	75.40	75.35	9.38	9.51[a]
w	$C_{21}H_{26}ClNO\cdot HCl$	$^{N}3.68$	3 99	—	—
x	$C_{20}H_{26}ClNO$	$^{N}4.22$	4.37	—	—
y	$C_{16}H_{17}Cl_2NO\cdot HCl$	$^{N}4.05$	3.79	—	—
z	$C_{17}H_{20}ClNO_2\cdot HCl$	$^{N}4.10$	4 00	—	—
aa	$C_{20}H_{26}ClNO_2$	$^{N}4.03$	4.17	—	—
bb	$C_{22}H_{22}ClNO$	75.09	75 00	6.30	6.60
bb_1	$C_{22}H_{22}ClNO\cdot HCl$	$^{Cl^-}9.13$	9.23		
cc	$C_{15}H_{18}ClNO_2$	$^{N}5.00$	4.75	—	—
dd	$C_{20}H_{20}ClNO\cdot HCl$	66.30	66.04	5.84	5.80[a]
ee	$C_{22}H_{31}ClN_2O$	70.46	70.35	8.34	9.47
ff	$C_{26}H_{39}ClN_2O$	72.44	72.61	9.12	9.47
gg	$C_{17}H_{18}ClNO$	$^{N}4.87$	4.66	—	—
gg_1	$C_{17}H_{18}ClNO\cdot HCl$	62.97	62.50	5.91	6.37[a]

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
hh	$C_{17}H_{18}ClNO$	$^{N}4.87$	4.64	—	—
ii	$C_{12}H_{16}ClNO_2$	$^{N}5.80$	5.38	—	—
jj	$C_{13}H_{18}ClNO_2$	$^{N}5.48$	5.19	—	—
kk	$C_{14}H_{20}ClNO_2$	$^{N}5.19$	4.89	—	—
ll	$C_{19}H_{30}ClNO$	$^{N}4.32$	4.62	—	—
mm	$C_{20}H_{28}ClNO$	71.94	71.75	8.45	8.31[a]
nn	$C_{18}H_{22}ClNO \cdot HCl$	63.54	63.46	6.52	6.83[a]
IIB a	$C_{12}H_{16}ClNO \cdot HCl$	$^{N}5.34$	5.44	—	—
b	$C_{16}H_{16}ClNO \cdot HCl$	$^{N}4.52$	4.25	—	—
c	$C_{19}H_{22}ClNO \cdot HCl$	$^{N}3.98$	4.09	—	—
e	$C_{21}H_{24}ClNO \cdot HCl$	$^{N}3.70$	3.88	—	—
f	$C_{20}H_{18}ClNO \cdot HCl$	$^{N}3.89$	3.80	—	—
g	$C_{17}H_{16}ClNO$	$^{N}4.90$	4.96	—	—
h₁	$C_{12}H_{14}ClNO_2 \cdot HCl$	$^{N}5.07$	5.16	—	—
i	$C_{13}H_{16}ClNO_2 \cdot HCl$	$^{N}4.83$	5.19	—	—
j	$C_{14}H_{18}ClNO_2 \cdot HCl$	$^{N}4.61$	4.80	—	—
m	$C_{21}H_{18}ClNO \cdot HCl$	67.74	68.08	5.14	5.08
n	$C_{17}H_{16}ClNO$	$^{N}4.90$	4.98	—	—
IIC a	$C_{19}H_{30}ClNO \cdot HCl$	63.32	63.62	8.67	8.35
b	$C_{17}H_{18}ClNO \cdot HCl$	$^{N}4.32$	$^{N}4.55$	—	—
IIIA a	$C_{16}H_{26}BrNO \cdot HCl$	52.68	52.92	7.46	7.20[a]
b	$C_{18}H_{30}BrNO$	$^{N}3.93$	4.02	—	—
c	$C_{18}H_{30}BrNO$	$^{N}3.93$	4.01	—	—
d	$C_{20}H_{34}BrNO$	$^{N}3.64$	4.04	—	—
e	$C_{22}H_{38}BrNO \cdot HCl$	$^{N}3.12$	2.87	—	—
f	$C_{24}H_{42}BrNO$	$^{N}3.18$	3.16	—	—
g	$C_{26}H_{46}BrNO$	$^{N}3.00$	3.02	—	—
h	$C_{16}H_{18}BrNO \cdot HCl$	53.87	53.58	5.37	5.42[a]
i	$C_{19}H_{24}BrNO \cdot HCl$	$^{Cl^-}8.90$	9.02	—	—
j	$C_{12}H_{16}BrNO_2$	50.35	50.24	5.64	5.61[a]
k	$C_{13}H_{18}BrNO_2$	$^{N}4.67$	$^{N}4.99$	—	—
l	$C_{14}H_{20}BrNO_2 \cdot HCl$	47.94	47.72	6.04	5.47[a]
m	$C_{14}H_{20}BrNO_2 \cdot HCl$	$^{N}4.00$	4.08	—	—
n	$C_{14}H_{20}BrNO_2 \cdot HCl$	$^{N}4.00$	4.29	—	—
o	$C_{14}H_{20}BrNO_2 \cdot HCl$	$^{N}4.00$	3.87	—	—
p	$C_{17}H_{24}BrNO \cdot HCl$	$^{N}3.74$	3.92	—	—
q	$C_{15}H_{16}BrNO$	$^{N}4.58$	4.51	—	—
IIIB	$C_{15}H_{24}BrNO \cdot HCl$	$^{N}3.99$	4.04	—	—
IIIC b	$C_{16}H_{16}BrNO \cdot HCl$	$^{N}3.95$	3.97	—	—
c	$C_{19}H_{22}BrNO \cdot HCl$	$^{Cl^-}8.94$	8.80	—	—
d₁	$C_{12}H_{14}BrNO_2 \cdot HCl$	$^{N}4.37$	4.22	—	—
e	$C_{13}H_{16}BrNO_2 \cdot HCl$	46.66	46.30	5.12	5.05[a]
f	$C_{14}H_{18}BrNO_2 \cdot HCl$	48.22	47.88	5.49	5.49[a]

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
g	$C_{14}H_{18}BrNO_2 \cdot HCl$	$^{N}4.02$	4.24	—	—
h₁	$C_{14}H_{18}BrNO_2 \cdot HCl$	$^{N}4.02$	3.91	—	—
i	$C_{17}H_{22}BrNO$	60.72	60.78	6.60	6.25
j	$C_{15}H_{14}BrNO$	$^{N}4.61$	4.48	—	—
IIID a	$C_{15}H_{22}BrNO \cdot HCl$	$^{Cl^-}10.17$	10.22	—	—
b	$C_{17}H_{26}BrNO \cdot HCl$	$^{N}3.72$	4.00	—	—
IVA a	$C_{12}H_{18}INO \cdot HCl$	$^{Cl^-}9.97$	10.01	—	—
b	$C_{14}H_{22}INO \cdot HCl$	$^{Cl^-}9.24$	9.41	—	—
c	$C_{16}H_{26}INO \cdot HCl$	$^{N}3.40$	3.31	—	—
d	$C_{12}H_{18}INO \cdot HCl$	$^{N}3.94$	3.65	—	—
e	$C_{18}H_{30}INO \cdot HCl$	49.15	49.34	7.11	7.43
f₁	$C_{24}H_{42}INO \cdot HCl$	$^{N}2.67$	$^{N}2.70$	—	—
g	$C_{16}H_{18}INO \cdot HCl$	$^{N}3.47$	3.76	—	—
h	$C_{12}H_{18}INO \cdot HCl$	$^{Cl-}9.65$	9.76	—	—
IVB a	$C_{14}H_{20}INO \cdot HCl$	$^{N}3.67$	3.63	—	—
b	$C_{16}H_{24}INO \cdot HCl$	$^{N}3.42$	3.38	—	—
c	$C_{16}H_{16}INO \cdot HCl$	$^{N}3.49$	3.26	—	—
d	$C_{13}H_{16}INO \cdot HCl$	$^{N}3.83$	3.78	—	—
V a	$C_{24}H_{42}FNO$	75.93	75.43	11.15	11.15
b	$C_{26}H_{46}FNO$	76.60	76.47	11.37	11.18
c	$C_{19}H_{24}FNO$	75.71	75.36	8.03	8.15
VI a	$C_{24}H_{42}ClNO$	$^{N}3.54$	3.46	—	—
b	$C_{16}H_{18}ClNO \cdot HCl$	$^{N}4.49$	4.66	$^{Cl^-}11.36$	11.59
VII a₁	$C_{18}H_{30}ClNO \cdot HCl$	$^{N}4.02$	3.68	—	—
b	$C_{24}H_{42}ClNO$	$^{N}3.54$	3.62	—	—
c₁	$C_{16}H_{18}ClNO \cdot HCl$	61.54	61.52	6.13	6.15^{a}
VIIIA a	$C_{16}H_{26}BrNO \cdot HCl$	$^{N}3.84$	4.08	—	—
b	$C_{18}H_{30}BrNO$	60.67	61.39	8.49	8.88^{a}
c	$C_{16}H_{18}BrNO \cdot HCl$	53.87	53.98	5.37	5.20^{a}
VIIIB	$C_{16}H_{16}BrNO \cdot HCl$	$^{N}3.95$	3.94	—	—
IX	$C_{16}H_{18}BrNO$	$^{N}4.37$	4.62	—	—
XA a	$C_{10}H_{14}INO$	$^{N}4.81$	4.65	—	—
b₁	$C_{12}H_{18}INO \cdot HCl$	$^{N}3.94$	4.18	—	—
c₁	$C_{14}H_{22}INO \cdot HCl$	$^{Cl^-}9.24$	9.32	—	—
d₁	$C_{16}H_{26}INO \cdot HCl$	46.67	46.39	6.61	6.68
e₁	$C_{16}H_{18}INO \cdot HCl$	$^{Cl^-}8.78$	8.90	—	—
XB	$C_{16}H_{16}INO \cdot HCl$	47.84	48.20	4.27	4.59

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
XI a	$C_{12}H_{18}INO \cdot HCl$	$^{Cl^-}$9.97	10.2	—	—
b	$C_{14}H_{22}INO \cdot HCl$	43.82	44.02	6.04	5.92
c	$C_{16}H_{26}INO \cdot HCl$	$^{Cl^-}$8.61	8.70	—	—
d	$C_{16}H_{18}INO \cdot HCl$	^{N}3.47	3.23	—	—
XII a	$C_{19}H_{33}NO_2$	74.22	73.88	10.82	10.61
b	$C_{20}H_{35}NO_2$	74.71	73.79	10.97	10.70
c	$C_{20}H_{35}NO_2$	74.71	74.71	10.97	10.93
XIII a	$C_{19}H_{33}NO$	78.29	78.35	11.41	11.40
b	$C_{21}H_{37}NO$	78.94	79.14	11.67	11.75
c	$C_{24}H_{43}NO$	^{N}3.87	3 68	—	—
d	$C_{30}H_{55}NO$	^{N}3.14	3.24	—	—
e	$C_{18}H_{29}NO$	78.49	78.58	10.61	11.03
f	$C_{22}H_{37}NO$	79.70	79.81	11.25	11.40
g	$C_{26}H_{47}NO$	^{N}3.59	3.81	—	—
h	$C_{24}H_{43}NO$	^{N}3.87	2.89	—	—
XIVA	$C_{22}H_{32}NO$	^{N}4.13	3.88	—	—
XIVB	$C_{20}H_{25}NO \cdot HCl$	$^{Cl^-}$10.68	11.12	—	—
XVA	$C_{24}H_{35}NO \cdot HCl$	73.91	73.76	9.31	9.11[a]
XVB	$C_{20}H_{23}NO_2$	77.64	77.31	7.49	7.33
XVIA a	$C_{19}H_{32}ClNO$	70.02	70.08	9.90	10.03
b	$C_{25}H_{44}ClNO$	^{N}3.42	3.47	—	—
c	$C_{17}H_{20}ClNO \cdot HCl$	^{N}4.29	4 51	^{X}21.74	21.46
XVIB	$C_{17}H_{18}ClNO \cdot HCl$	63.00	63.12	5.91	5.86[a]
XVIIA a	$C_{19}H_{32}ClNO$	^{N}4.30	4.52	—	—
b	$C_{25}H_{44}ClNO$	^{N}3.42	3.50	—	—
c	$C_{17}H_{20}ClNO \cdot HCl$	^{N}4.29	4.12	—	—
XVIIB	$C_{17}H_{18}ClNO \cdot HCl$	^{N}4.31	4.27		
XVIII a	$C_{19}H_{32}ClNO$	^{N}4.30	4.24	—	—
b	$C_{17}H_{20}ClNO$	^{N}4.83	4.77	—	—
XIX a	$C_{25}H_{44}ClNO$	^{N}3.42	3.34	—	—
b	$C_{17}H_{20}ClNO \cdot HCl$	^{N}4.29	4.20	$^{Cl^-}$10.87	10.91
XXA a	$C_{14}H_{22}ClNO_2 \cdot HCl$	^{N}4.54	4.27	—	—
b	$C_{20}H_{34}ClNO_2 \cdot HCl$	^{N}3.57	3.28	—	—
c	$C_{18}H_{22}ClNO_2 \cdot HCl$	60.68	60.46	6.51	6.80[a]
d	$C_{19}H_{24}ClNO_2 \cdot HCl$	^{N}3.78	3.95	—	—
XXB	$C_{18}H_{20}ClNO_2 \cdot HCl$	^{N}3.95	4.12	—	—

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl^-)		H	
		CALC'D	FOUND	CALC'D	FOUND
XXI	$C_{19}H_{32}ClNO_2 \cdot HCl$	60.30	60.59	8.79	8.66
XXII a	$C_{17}H_{28}BrNO$	^{N}4.09	4.24	—	—
b	$C_{19}H_{32}BrNO$	61.61	62.00	8.71	8.98
c	$C_{25}H_{44}BrNO$	^{N}3.08	3.20	—	—
d	$C_{17}H_{20}BrNO$	^{N}4.19	3.89	—	—
XXIII	$C_{19}H_{32}BrNO$	^{N}3.78	3.97	—	—
XXIV a	$C_{17}H_{28}BrNO \cdot HCl$	53.90	53.89	7.72	7.69
b	$C_{25}H_{44}BrNO$	66.06	66.05	9.76	9.56^{a}
XXVA a	$C_{12}H_{17}Cl_2NO \cdot HCl$	$^{Cl^-}$11.87	11.98	—	—
a_1	$C_{18}H_{20}Cl_2N_4O_8$	^{N}11.41	11.28	—	—
b	$C_{16}H_{25}Cl_2NO$	60.37	60.03	7.92	7.82
c	$C_{18}H_{29}Cl_2NO$	^{N}4.05	4.42	—	—
d	$C_{24}H_{41}Cl_2NO$	^{N}3.25	3.39	—	—
e	$C_{16}H_{17}Cl_2NO \cdot HCl$	55.43	55.42	5.24	5.42
f	$C_{22}H_{21}Cl_2NO \cdot HCl$	^{N}3.33	3.35	—	—
g	$C_{17}H_{19}Cl_2NO \cdot HCl$	^{N}3.88	3.76	—	—
h	$C_{16}H_{25}Cl_2NO \cdot HCl$	^{N}3.95	3.98	$^{Cl^-}$10.00	10.13
i	$C_{20}H_{29}Cl_2NO \cdot HCl$	^{N}3.44	3.53	—	—
XXVB	$C_{22}H_{19}Cl_2NO \cdot HCl$	^{N}3.33	3.46	—	—
XXVI a	$C_{16}H_{25}Cl_2NO \cdot HCl$	^{N}3.95	4.19	—	—
b	$C_{24}H_{41}Cl_2NO_2 \cdot HCl$	61.73	61.85	9.07	8.80^{a}
XXVII a	$C_{24}H_{41}Cl_2NO \cdot HCl$	^{N}3.00	3.28	$^{Cl^-}$7.59	7.37
b	$C_{16}H_{17}Cl_2NO$	^{N}4.52	4.89	—	—
XXVIII a	$C_{16}H_{25}Cl_2NO \cdot HCl$	54.17	54.15	7.39	7.35
b	$C_{16}H_{17}Cl_2NO \cdot HCl$	55.43	55.66	5.23	5.10^{a}
XXIX	$C_{24}H_{41}Cl_2NO \cdot HCl$	61.73	61.40	9.07	8.87^{a}
XXXA a	$C_{12}H_{17}Br_2NO \cdot HCl$	37.19	37.30	4.68	4.70^{a}
b	$C_{18}H_{29}Br_2NO \cdot HCl$	^{N}2.97	2.83	$^{Cl^-}$7.52	7.68
c	$C_{16}H_{17}Br_2NO$	^{N}3.51	3.78	—	—
XXXB	$C_{16}H_{15}Br_2NO \cdot HCl$	$^{Cl^-}$8.18	8.09	—	—
XXXIA	$C_{18}H_{21}NO$	^{N}5.05	4.85	—	—
XXXIB	$C_{18}H_{27}NO_2 \cdot HCl$	$^{Cl^-}$10.88	10.80	—	—

TABLE II—*Continued*

COMPOUND NO.		EMPIRICAL FORMULA	C (OR N OR Cl^-)		H	
			CALC'D	FOUND	CALC'D	FOUND
XXXIIA	a	$C_{16}H_{27}NO$	77.05	76.69	10.91	10.43
	b	$C_{20}H_{35}NO \cdot HCl$	^{N}4.10	4.15	$^{Cl^-}$10.37	10.44
	c	$C_{17}H_{27}NO \cdot HCl$	68.55	68.32	9.48	9.38^{a}
	d	$C_{16}H_{25}NO_2 \cdot HCl$	64.09	63.68	8.74	8.44
	e	$C_{19}H_{32}NO$	^{N}4.81	4.92	—	—
XXXIIB	a	$C_{17}H_{25}NO \cdot HCl$	69.01	68.71	8.86	9.01^{a}
	b	$C_{16}H_{23}NO_2 \cdot HCl$	64.52	64.49	8.12	7.82^{a}
XXXIII	a	$C_{17}H_{27}Cl_2NO$	^{X}21.34	21.24	—	—
	b	$C_{19}H_{31}Cl_2NO$	^{X}19.68	19.53	—	—
	c	$C_{25}H_{43}Cl_2NO \cdot HCl$	62.42	62.84	9.22	8.90^{a}
	d	$C_{17}H_{19}Cl_2NO \cdot HCl$	56.65	56.89	5.31	5.78^{a}
XXXIV	a	$C_{17}H_{27}Cl_2NO$	^{N}4.22	4.42	—	—
	b	$C_{19}H_{31}Cl_2NO$	^{X}19.68	19.70	—	—
	c	$C_{25}H_{43}Cl_2NO$	^{X}15.96	15.82	—	—
	c_1	$C_{25}H_{43}Cl_2NO \cdot HCl$	62.42	61.95	9.22	9.10^{a}
XXXVA	a	$C_{19}H_{32}ClNO$	^{N}4.30	4.01	—	—
	b	$C_{25}H_{44}ClNO$	^{N}3.42	3.68	—	—
	c	$C_{17}H_{20}ClNO$	70.45	70.14	6.96	6.90^{a}
	d	$C_{14}H_{20}ClNO \cdot HCl$	^{N}4.83	4.63	$^{Cl^-}$12.22	12.31
	e	$C_{18}H_{30}ClNO$	69.31	69.80	9.70	10.23
	f	$C_{20}H_{34}ClNO$	70.66	70.98	10.08	10.40
	g	$C_{20}H_{34}ClNO$	70.66	71.02	10.08	10.32
	h	$C_{20}H_{26}ClNO$	72.38	72.48	7.90	7.93
	i	$C_{17}H_{26}ClNO$	^{N}4.74	4.92	—	—
	i_1	$C_{17}H_{26}ClNO \cdot HCl$	$^{Cl^-}$10.67	10.51	—	—
	j	$C_{21}H_{26}ClNO \cdot HCl$	^{N}3.68	3.91	—	—
XXXVB	a	$C_{17}H_{18}ClNO \cdot HCl$	^{N}4.32	3.96	—	—
	b	$C_{14}H_{18}ClNO$	^{N}5.56	5.47	—	—
	b_1	$C_{14}H_{18}ClNO \cdot HCl$	^{N}4.86	5.09	—	—
	c	$C_{20}H_{24}ClNO \cdot HCl$	^{N}3.82	4.06	—	—
	d	$C_{17}H_{24}ClNO \cdot HCl$	^{N}4.24	3.86	—	—
	e	$C_{21}H_{24}ClNO \cdot HCl$	^{N}3.70	3.44	—	—
XXXVI	b	$C_{19}H_{32}BrNO$	^{N}3.78	3.69	—	—
XXXVII		$C_{18}H_{22}BrNO$	^{N}4.02	3.97	—	—
XXXVIIIA	a	$C_{20}H_{35}NO$	78.63	78.28	11.55	11.45
	b	$C_{17}H_{27}NO$	78.11	78.43	10.41	9.96
	c	$C_{16}H_{25}NO_2 \cdot HCl$	64.09	64.07	8.74	8.78
	d	$C_{23}H_{39}NO$	^{N}4.20	4.09	—	—
	e	$C_{19}H_{33}NO$	^{N}4.81	4.42	—	—
	f	$C_{20}H_{35}NO \cdot HCl$	$^{Cl^-}$10.37	10.63	—	—

TABLE II—*Concluded*

COMPOUND NO.	EMPIRICAC FORMULA	C (OR N OR Cl^-)		H	
		CALC'D	FOUND	CALC'D	FOUND
XXXVIIIB a	$C_{17}H_{25}NO \cdot HCl$	69.01	68.88	8.86	8.72
b	$C_{16}H_{23}NO_2 \cdot HCl$	64.51	64.85	8.12	8.62[a]
XXXIXA a	$C_{22}H_{39}NO \cdot HCl$	71.41	71.48	10.90	10.75
b	$C_{23}H_{39}NO \cdot HCl$	72.31	72.59	10.55	10.65
c	$C_{22}H_{37}NO_2 \cdot HCl$	68.81	68.81	9.98	9.78
XXXIXB	$C_{23}H_{41}NO \cdot HCl$	71.93	72.19	11.02	11.35
XXXIXC a	$C_{23}H_{37}NO \cdot HCl$	72.69	72.51	10.08	10.28
b	$C_{22}H_{35}NO_2 \cdot HCl$	69.17	68.76	9.50	9.67
XXXIXD	$C_{21}H_{35}NO \cdot HCl$	71.25	71.41	10.25	10.50

[a] Additional Analyses.

FORMULA NO.	CALC'D N	FOUND N	FORMULA NO.	CALC'D N	FOUND N	FORMULA NO.	CALC'D N	FOUND N
IA f	3.96	4.03	j	4.90	4.76	XXIX	3.00	3.11
IIA d	4.49	4.61	l	4.00	4.03		Cl^-7.59	7.56
i	3.54	3.33	IIIC e	4.19	4.07	XXXA a	3.62	3.86
k	3.10	3.23	f	4.02	3.95	XXXIIA c	Cl^-11.91	11.90
t	3.95	4.35	VIIC_1	Cl^-11.35	11.50	XXXIIB a	4.74	4.22
v	3.26	3.58	VIIIA b	3.93	4.43	b	4.70	4.54
dd	3.87	4.06	c	Cl^-9.94	10.19		Cl^-11.91	11.84
gg_1	Cl^-10.93	11.18	XVA	Cl^-9.09	9.13	XXXIII c	C^{-1}7.37	7.46
mm	4.20	4.49	XVIB	4.32	4.23	d	Cl^-9.83	9.84
nn	4.12	4.39	XXA c	3.93	4.10	XXXIV c_1	2.91	3.19
			XXIV b	3.08	3.28			
IIIA a	3.84	3.93	XXVI b	3.00	3.07		Cl^-7.37	7.62
	Cl^-9.72	9.83		Cl^-7.59	7.71	XXXVA c	4.83	4.65
h	3.93	3.85	XXVIII b	4.04	4.34	XXXVIIIB b	4.72	4.67

[N] These analyses are for nitrogen rather than carbon and hydrogen.

[Cl^-] These analyses are for chloride ion (titration method).

[X] These figures represent the total chlorine content, and were carried out by Miss Elizabeth Wilson, using the nickel-aluminum alloy reduction method (91).

SUMMARY

The discovery of moderate antimalarial activity in the nuclear substituted α-phenyl-β-dialkylaminoethanols led to an extensive investigation designed to evaluate the effect of: (a) the phenyl nucleus itself, (b) variation in the alkyl groups on nitrogen, (c) substitution of halogen in the phenyl nucleus, (d) substitution of other groups including alkyl and alkoxyl, (e) the location of the substituent in the nucleus, (f) substitution of two or more groups in different nuclear positions, (g) lengthening the amino alcohol chain to three, four, six,

and twelve carbons, and (h) the separation of the alcoholic hydroxyl and the *tert.*-amino group by three carbons instead of two.

A total of 184 amino alcohols and 55 amino ketones were synthesized and submitted for screening tests against avian malaria. These compounds included examples of fifty variations in the phenyl nucleus and over sixty variations in the N,N-dialkyl groups on the nitrogen. A large number of N-alkyl-N-benzylamino types were made.

Most of the drugs were made by condensation of the α-bromoacetophenone and the appropriate secondary amine to give the *tert.*-amino ketones, and by reduction of these with aluminum isopropoxide. The alternative path used in a few cases was the reduction of the α-bromoacetophenone to the bromohydrin and condensation directly with the secondary amine.

Most of the bromomethyl ketones which were not available were made by bromination of the appropriate acetophenone; a few were made from the acids through the acid chlorides by diazomethylation and treatment with hydrobromic acid. Some of the methyl ketones were made by the Friedel-Crafts reaction on the appropriate benzene derivative; and in two cases chloromethyl ketones were made by this reaction. A few methyl ketones were made by addition of methylmagnesium iodide to the appropriate nitrile, and one was made by oxidation of the secondary alcohol which had been obtained from the aldehyde by addition of methylmagnesium iodide.

Two drugs were prepared both through the bromohydrin (the more convenient path) and through the amino ketone. The latter synthesis demonstrated the mode of the ethylene oxide ring cleavage involved.

In the distillation of the amino alcohols of high molecular weight hydramine fission often occurred to some extent. Also in some cases the partial displacement of ortho or para halogen was noted.

The following *mono-substituents* were introduced into the nucleus of the α-phenyl-β-dialkylaminoethanols: 4-chloro, 4-bromo, 4-iodo, 4-fluoro, 3-chloro, 2-chloro, 3-bromo, 2-bromo, 3-iodo, 2-iodo, 4-methoxy, 4-ethoxy, 4-(*n*-butoxy), 4-isopropyl, 4-*n*-hexyl, 4-cyclohexyl, 4-*n*-decyl, 4-*n*-dodecyl, 4-benzyl, and 4-(β-phenylethyl).

The following *di-substitutions* were made: 4-chloro-3-methyl, 3-chloro-4-methyl, 2-chloro-4-methyl, 2-chloro-5-methyl, 3-chloro-6-methoxy, 3-chloro-4-ethoxy, 4-bromo-3-methyl, 4-bromo-2-methyl, 3-bromo-4-methyl, 3,4-dichloro, 2,4-dichloro, 2,5-dichloro, 3,5-dichloro, 2,6-dichloro, 3,5-dibromo, 2,4-di-(isopropyl), and 5-isopropyl-2-methyl.

The following *tri-substitutions* were made: 2,4-dichloro-3-methyl and 3,4-dichloro-6-methyl.

α-4-Chlorophenyl-β-dialkylamino alcohols were made with amino alcohol chains of 3, 4, and 6 carbons; also α-4-bromophenyl analogs of the first of these types. In the α-phenyl-β-dialkylaminohexanols, the following substituents were employed: none, 4-ethyl, 4-isopropyl, and 4-*tert.*-butyl. The series of α-phenyl-β-dialkylaminododecanols carried no nuclear substituents.

In the α-4-chlorophenyl-β-aminoethanol series the following dialkyl substitutions on the nitrogen were employed: diethyl, di-*n*-butyl, di-isobutyl, diamyl, di-isoamyl, dihexyl, diheptyl, dioctyl, di-(2-ethylhexyl), dinonyl, didecyl, di-undecyl, didodecyl, and ditridecyl. The following N-alkyl-N-benzyl groups were employed: benzylmethyl, benzylethyl, benzylpropyl, benzylisopropyl, benzylbutyl, benzyl-(2-methylpropyl), benzylamyl, benzyloctyl, benzyldodecyl, benzylcyclohexyl, (α-butylbenzyl)methyl, 4-chlorobenzylmethyl, 4-methoxy-benzylmethyl, 4-methoxybenzylbutyl, and dibenzyl; also the following analogous types: (α-furylmethyl)ethyl, (α-naphthylmethyl)methyl, benzyl(3-diethylamino-propyl), benzyl(3-dibutylaminopropyl), and N-tetrahydroisoquinolyl. The following miscellaneous groupings were used: morpholinyl, 2-methylmorpholinyl, 2,6-dimethylmorpholinyl, 2-(*n*-hexyl) piperidyl, *trans*-dodecahydrocarbazyl, N-methyl-N-phenyl, N-butyl-N-phenyl, benzylphenyl, and tetrahydroquinolyl.

In certain series other than the 4-chlorophenyl the following -NR_2 groups, in addition to the above, were employed: monooctyl, 2-chlorobenzylmethyl, 2-ethylmorpholinyl, 3-ethylmorpholinyl, and 3,3-dimethylmorpholinyl.

Representative β-*tert.*-amino ketones were made by the Mannich reaction on the following: 4-chloro- and 4-bromoacetophenones, and laurophenone.

The following γ-*tert.*-amino alcohols were made by reduction of the β-*tert.*-amino ketones: α-(4-bromophenyl)-γ-dialkylaminopropanol, and α-phenyl-β-dialkylaminomethylhexanol.

The antimalarial activities of the majority of these drugs ranged from Q = 0.1 to Q = 0.5 and in a few cases reached Q = 1 against *gallinaceum* in the chick, and in one case Q = 2 against *lophurae* in the duck. The highest activities were found in the following types: 2,4-dichloro, 3,4-dichloro, 2,5-dichloro and 4,5-dichloro-2-methyl.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

MECHANISM OF THE CONDENSATION OF NITRO ALKANES WITH ALDEHYDES[1]

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Priebs (1) in 1884 condensed benzaldehyde with nitromethane but ten years elapsed before Louis Henry and his pupils (2) carried out extensive study of this reaction and showed that this aldol-type condensation could be extended to aliphatic aldehydes with facility, that dehydration of the nitro alcohol could be prevented, and also that more than one mole of aldehyde could react with suitable nitro alkanes. After the discovery of vapor-phase nitration (3) made all the nitro alkanes potentially available, Vanderbilt and Hass (4) improved and extended Henry's methods. Kamlet (5) devised a useful method of carrying out the reaction when he introduced the expedient of preparing the bisulfite addition product of the aldehyde (benzaldehyde) and the sodium salt of the nitro alkane and causing them to react, a method which has also been extended in this laboratory.

All the prior work was chiefly concerned with ascertaining the limits and usefulness of the reaction rather than with its mechanism. This work is concerned with ascertaining the mechanism of the condensation.

As is the case in the usual aldol condensation, the formation of a nitro alcohol requires the presence of a catalyst. The reaction involved is the addition of one of the hydrogens (in this case a hydrogen from the carbon atom holding the nitro group) to the carbonyl group of the aldehyde.

A salt of a primary nitro paraffin may react directly and rapidly with an aldehyde to yield the salt of a nitro alcohol.

$$RCHO + CH_2{=}NO_2Na \rightarrow RCHOHCH{=}NO_2Na$$

According to the resonance concept, the carbon atom of the carbonyl group bears a partial positive charge while the negative charge of the nitronic anion exists partially on the alpha carbon atom. These carbon atoms therefore attract each other, and the condensation consists essentially in their union.

If a salt of a secondary nitro paraffin is employed, the situation is somewhat different. The equilibrium

$$R'CHO + R_2C = NO_2Na \rightleftarrows R'CHONaCR_2NO_2$$

can not proceed very far to the right because the tertiary nitro group present in the nitro alcohol can no longer form a salt. The alcoholic hydroxyl group is a much feebler acid than a nitronic acid. As soon as a little alkalinity is built up the reaction must stop. In fact, Vanderbilt and Hass (4) showed that such a nitro alcohol can be split practically quantitatively by adding an equivalent of base.

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According to this concept of the reaction, the function of the bisulfite in the Kamlet process is to prevent this accumulation of base and thus to allow the reaction to proceed virtually to completion. The formation of an addition compound between the bisulfite and aldehyde is entirely a secondary matter and of no essential importance to the reaction. Therefore, the addition of any other substance sufficiently acidic to neutralize the solution should also bring about the reaction. Strong mineral acids, however, are known to yield aldehydes and ketones when they react with salts of nitronic acids and for this reason their use did not appear advisable, but a weaker acid such as acetic or carbonic seemed suitable.

To test this hypothesis the condensations have been carried out with several different materials serving as acidifying agents.

EXPERIMENTAL

The nitro paraffins used in this study were obtained from Commercial Solvents Corporation and, with the exception of nitromethane which contained a trace of water, were practically pure as received but, nevertheless, all of them were redistilled through a packed column filled with glass helices. The aldehydes were of the best commercial grade and each was distilled immediately before using.

All the condensations were carried out in the same general manner. An aldehyde and a weak acid were added simultaneously to a solution containing the salt of a nitronic acid. Reaction took place rapidly, accompanied by a slight evolution of heat. The nitro alcohols obtained were light amber oils with a characteristic pleasing odor. They boiled over a narrow range and their constants agreed well with those more carefully determined previously in this laboratory.

Condensation of 2-nitrobutane and n-butyraldehyde using sodium bisulfite as the acidifying agent. 2-Nitrobutane (103 g., 1 mole) was gradually added in small portions to a hot, agitated solution of sodium hydroxide (41 g., 1.025 mole) in 300 ml. of water. The nitro alkane dissolved slowly and it was necessary to warm the mixture to maintain it at 60°. At the same time, *n*-butyraldehyde (72 g., 1 mole) was dissolved in a solution of sodium bisulfite (115 g., 1.10 mole) in 400 ml. of water. Then, with agitator and reflux condenser in position and the temperature of the sodium nitrobutane solution at 60°, the solution of bisulfite addition product was slowly added over a period of approximately two hours, maintaining a temperature of 60°.

The reaction mixture, from which some oil had already separated, was agitated vigorously overnight. The orange-colored oil layer was separated, the aqueous layer was extracted with two 100-ml. portions of ether, and the ether solution was combined with the oil layer. The combined ether solutions were washed with sodium bisulfite solution to remove aldehyde. Ether was removed by evaporation and the residue was distilled 3-Methyl-3-nitro-4-heptanol, 17 g., b. 117–119°. at 10 mm., resulted. Yield of nitro alcohol, 27.8%. Yield of the same alcohol by the Vanderbilt-Hass method, 40.0%.

Condensation of 2-nitropropane with n-butyraldehyde using acetic acid as the acidifying agent. 2-Nitropropane (45 g., 0.5 mole) was gradually added to a well agitated solution of sodium hydroxide (20.5 g., 0.52 mole) in 80 ml. of water. The temperature was not allowed to exceed 50°. When formation of the salt was complete, a mixture of *n*-butyraldehyde (43.2 g., 0.6 mole) and glacial acetic acid (32 g., 0.53 mole) was added dropwise over a period of forty-five minutes with good agitation. The suspension was agitated and maintained at 50° for two hours after the material had all been added. The solution was cooled and the product was separated as already described. Light yellow, oily 2-methyl-2-nitro-1-hexanol, 24 g., b. 103–106° at 8 mm., resulted. Yield of the nitro alcohol, 86.2%; conversion 46%. Yield by the Vanderbilt-Hass method, 65%.

Using similar conditions and the same molar proportions, the following reactions were carried out with results as indicated.

NITRO PARAFFIN	ALDEHYDE	CONVERSION %	YIELD %	YIELD, METHOD OF VANDERBILT-HASS %
1-Nitropropane	*n*-Butyraldehyde	63.8	88.4	96.5
2-Nitropropane	*n*-Butyraldehyde	46.0	86.2	65.0
2-Nitropropane	Isobutyraldehyde	14.2	30.4	11.0
2-Nitrobutane	Isobutyraldehyde	9.2	36.4	3.0

Condensation of 2-nitropropane and n-butyraldehyde using carbon dioxide as the acidifying agent. The amounts were the same as indicated in the preceding experiment except that no acetic acid was used. Instead, the agitated solution of the salt of the nitro paraffin was warmed to 45° and carbon dioxide was passed into it. After the carbon dioxide (generated from dry-ice) had been bubbling in about one minute, addition of aldehyde was begun. It was added dropwise over about twenty minutes. After carbon dioxide had been passed into the mixture for about three hours, reaction appeared to be complete and the mixture was allowed to stand for about eighteen hours. The product was mixed with 400 ml. of water and extracted with two 30-ml. portions of ether. This was processed as already described and collected over the same boiling range; 2-methyl-2-nitro-3-hexanol, 44.3 g., resulted; conversion, 55.0%.

Condensation of nitroethane and benzaldehyde using carbon dioxide as the acidifying agent. Nitroethane (82.5 g., 1.1 moles) was dissolved in a solution of sodium hydroxide (45 g., 1.12 moles) in 100 ml. of water. The solution was cooled to 65° and benzaldehyde (106 g., 1 mole) was added. The suspension was stirred with a powerful agitator until a fine emulsion existed; then carbon dioxide was passed in at a fairly rapid rate. The temperature was allowed to rise to 75° and was maintained at that level for two hours. The mass was allowed to stand twenty-four hours. Then the semi-solid contents of the flask were poured into water to dissolve the precipitated sodium bicarbonate.

The oil layer was separated, the aqueous layer was extracted with ether, and the extract was added to the oil layer. This was processed in the usual way. 2-Nitro-1-phenyl-1-propanol, 85 g., b. 120–126° at 2 mm., resulted. Conversion to nitro alcohol, 48%; yield, 91%.

ACKNOWLEDGMENTS

The authors wish to acknowledge assistance from Commercial Solvents Corporation, which provided financial aid to this program as Purdue Research Foundation Fellowship No. 38, and to Dr. Elizabeth F. Riley, who assisted in the preparation of this manuscript.

SUMMARY

It has been found that nitro alcohols may be produced rapidly and in good yields by adding an acidic substance such as glacial acetic acid, sodium bisulfate or carbon dioxide (as well as the sodium bisulfite previously reported by Kamlet) to an aqueous solution containing a salt of a nitronic acid and also an aldehyde.

A mechanism for the condensation is proposed which postulates union between the positive carbon atom of the carbonyl group and the negative alpha carbon

atom of the nitronic anion. According to this hypothesis, the function of the acid is, in the case of primary nitro paraffins, to liberate the nitro alcohol from its salt and in the case of secondary nitro paraffins to prevent the accumulation of base which reverses the addition.

LAFAYETTE, IND.

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[Contribution from the United States Department of Agriculture, Agricultural Research Administration, Bureau of Entomology and Plant Quarantine]

ANHYDROUS FERRIC CHLORIDE AS A REARRANGEMENT CATALYST FOR SOME CHLORINATED DIPHENYLETHANES

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Received February 17, 1947

During the course of the investigation of the catalytic dehydrochlorination of DDT and related compounds (1), it was noted that 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (I), known as TDE or DDD, behaved abnormally when heated with anhydrous ferric chloride. By analogy with DDT, (I) should loose a mole of hydrogen chloride to form 1-chloro-2,2-bis(*p*-chlorophenyl)ethylene (II). It was found that when (I) was heated at 115–120° with small amounts of anhydrous ferric chloride from 0.1 to 1.0 mole of hydrogen chloride was evolved. Further investigation showed that, when the heating was carried out at the melting point of (I) in the presence of about 6% of catalyst, a minimum of hydrogen chloride was evolved, and rearrangement took place to form a compound which melted at 227–228°, and which proved to be isomeric with the starting material. The rearrangement product was found to be identical with a tetrachlorobibenzyl, which was prepared by the addition of chlorine to 4,4′-dichlorostilbene. This shows that the rearrangement involves the shifting of a chlorine atom and a chlorophenyl group, and establishes III or IV as the structure of the rearrangement product.

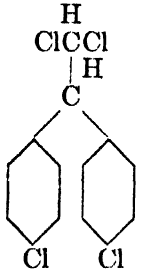
Rearrangements of this general type, involving a shift of the phenyl group to change an unsymmetrical diphenylethane into a symmetrical one, have been observed by Elbs (2). He showed that with zinc dust and ammonium hydroxide, as well as by distillation with zinc dust, α-diphenyltrichloroethane derivatives were rearranged and simultaneously dehydrochlorinated to form substituted stilbenes. Recently Forrest *et al.* (3) demonstrated a similar migration of the phenyl group when DDT was reduced in boiling alcohol with zinc and concentrated hydrochloric acid. In these examples some of I was obtained in the products of the reduction of DDT, indicating that the formation of the stilbenes may proceed through this intermediate compound.

When the tetrachlorobibenzyl, obtained by rearrangement, was refluxed with alcoholic caustic, 1 mole of hydrogen chloride was eliminated and a trichlorostilbene of melting point 59–60° was obtained. The same compound was prepared by this process, starting with the synthetic tetrachlorobibenzyl.

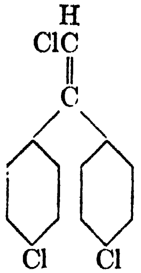
An isomeric trichlorostilbene of melting point 95–96° was obtained by heating III at 200° with a small amount of anhydrous ferric chloride. Both of these trichlorostilbenes gave a strong unsaturation test with tetranitromethane, and the melting point was depressed when the two were mixed. These compounds may be represented by formulas V and VI, to which, on the basis of melting points, the low-melting form may be assigned the *cis* form (V) and the high-melting form the *trans* form (VI) (4).

Both of these trichlorostilbenes were oxidized with chromic acid to 4,4′-dichlorobenzil. The identity of this compound was established by determination of the mixed melting point with authentic material, and by preparation of 2-(4-chlorophenyl(-3-(4-chlorophenyl)quinoxaline, melting point 187–188°, by reaction with *o*-phenylenediamine.

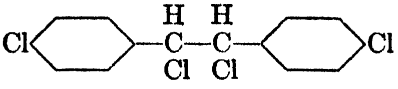
In connection with the chlorination of 4,4′-dichlorostilbene to obtain the tetrachlorobibenzyl, melting at 227–228°, a second isomer, melting at 95–96°, was isolated by concentration of the mother liquors. By analogy with the dichlorostilbenes, prepared by the chlorination of stilbene (8), the high-melting isomer



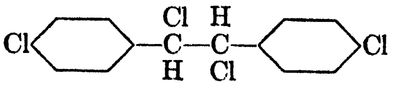
I



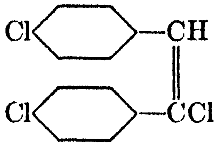
II



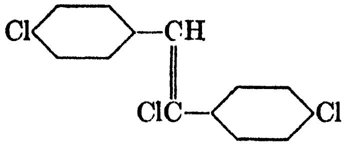
III



IV



V



VI

has been designated *meso*-α,α',4,4′-tetrachlorobibenzyl (III) and the low-melting isomer *dl*-α,α',4,4′-tetrachlorobibenzyl (IV). This *dl*-isomer was converted into the *meso*-isomer by melting the former in contact with a small amount of anhydrous ferric chloride.

The same type of catalytic isomerization was found to occur when *dl*-dichlorostilbene was isomerized into *meso*-dichlorostilbene by the same process. This isomerization is known to be partially effected by heating the *dl*-isomer at 200° (5), but with the catalyst the transformation occurred at 105–115° during the course of ten minutes.

The action of anhydrous ferric chloride in isomerizing the *dl*-isomers into *meso*-isomers undoubtedly accounts for the fact that only the *meso*-isomer could be isolated from the rearrangement products of I.

Since anhydrous ferric chloride is known to remove 1 mole of hydrogen chloride from DDT at 110° to form 1,1-dichloro-2,2'-bis(*p*-chlorophenyl)ethylene, an attempt was made to isomerize the latter compound with anhydrous ferric chloride. The fact that no rearrangement product could be isolated opens up the possibility of using this technique to detect I in the presence of DDT.

EXPERIMENTAL

Rearrangement of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane. An intimate mixture of 5 g. of I, m.p. 109–110°, and 0.3 g. of sublimed anhydrous ferric chloride (E&A, C.P.) was placed in a test tube and heated in an oil-bath at 110 ± 2° for one hour. A small amount of hydrogen chloride was evolved, and after about fifteen minutes of heating the mass set solid with crystals. The cooled material was transferred to a mortar with 50 ml. of glacial acetic acid and triturated at room temperature. The mixture was filtered and washed with a small amount of acetic acid and then with water. The yield of the crude product, after drying in a vacuum at room temperature was 2.9 g. of material that melted with decomposition at 185°. Repeated recrystallizations from acetic acid, following hot filtration, yielded a colorless product that separated in diamond-shaped crystals which melted at 227–228°. No yellow color was given with tetranitromethane.

Anal. Calc'd for $C_{14}H_{10}Cl_4$: C, 52.53: H, 3.15; Cl, 44.32; mol. wt., 320.06.

Found: C, 52.45, 52.67; H, 3.22, 3.20; Cl, 44.33; mol. wt., 317 (Rast).

When this rearrangement was carried out in a U-tube connected to an absorption bottle containing water to absorb the liberated hydrogen chloride, the amount obtained ranged from 0.1 to 0.5 mole with individual runs.

Trans-α,4,4'-trichlorostilbene. One gram of the tetrachlorobibenzyl, prepared by rearrangement, was heated in an oil-bath at 210°. A small amount of crude rearrangement product or a trace of anhydrous ferric chloride may have to be added to start the decomposition at this temperature. The dehydrochlorination had finished at the end of five minutes' heating. The residue crystallized when cooled, and when recrystallized from alcohol yielded light yellow needles that melted at 95–96°. It was necessary to remove a red amorphous powder by hot filtration of the alcoholic solution. This powder probably represents a polymerization product. With tetranitromethane a deep yellow-orange color was obtained.

Anal. Calc'd for $C_{14}H_9Cl_3$: C, 59.29; H, 3.20; Cl, 37.51.

Found: C, 59.15; H, 3.14; Cl, 36.75.

When this decomposition was carried out in a U-tube and the evolved gases were drawn through an absorption bottle containing water, 1.01 mole of hydrogen chloride was obtained.

Cis-α,4,4'-trichlorostilbene. One gram of the tetrachlorobibenzyl, prepared by rearrangement, was refluxed for one hour in 50 ml. of alcohol and 2 g. of potassium hydroxide. The cooled solution was diluted with water and extracted with ether. The ether solution was washed with water and then evaporated to dryness on the steam-bath. The residue crystallized as needles from alcohol. After drying in a vacuum at room temperature, the product melted at 59–60° and gave a deep yellow color with tetranitromethane. When this product was mixed with *trans-α*,4,4'-trichlorostilbene, the melting point was 50–70°.

Anal. Calc'd for $C_{14}H_9Cl_3$: C, 59.29; H, 3.20; Cl, 37.51.

Found: C, 59.55; H, 3.40; Cl, 37.98.

Oxidation of cis-α,4,4'-trichlorostilbene with chromic oxide. A solution of 0.4 g. of *cis-α*,4,4'-trichlorostilbene (m.p. 59–60°) in 2 ml. of refluxing acetic acid was oxidized by the slow addition of 0.2 g. of chromic oxide. Vigorous reaction occurred with each addition of chromic oxide. Refluxing was continued for one hour. Crystals separated from the cooled solution Water was added to complete the crystallization. The product separated from acetone as light yellow needles and melted at 196–197°. No depression of melting point occurred when mixed with 4,4'-dichlorobenzil (6).

2-(4-Chlorophenyl)-3-(4-chlorophenyl)quinoxaline. A solution of 28 mg. of the 4,4′-dichlorobenzil, obtained from the above oxidation, and 11 mg. of *o*-phenylenediamine in 1 ml. of acetic acid was refluxed for one hour. When the reactants were cooled to room temperature, 25 mg. of colorless needles separated. When recrystallized from acetic acid, they melted at 187–188°. They showed no depression of melting point when mixed with a quinoxaline prepared by the same procedure from authentic 4,4′-dichlorobenzil.

Anal. Calc'd for $C_{20}H_{12}Cl_2N_2$: C, 68.39; H, 3.44.
Found: C, 68.48; H, 3.53.

Oxidation of trans-α,4,4′-trichlorostilbene with chromic oxide. A solution of 0.4 g. of *trans*-α,4,4′-trichlorostilbene (m.p. 95–96°) in 2 ml. of acetic acid was oxidized by the procedure used for *cis*-α,4,4′-trichlorostilbene. The product separated as colorless needles, which melted at 196–197° and did not depress the melting point when mixed with authentic 4,4′-dichlorobenzil (6).

The 2-(4-chlorophenyl)-3-(4-chlorophenyl)quinoxaline prepared from this material, as outlined above, melted at 187–188°, and no depression of melting point was observed when the product was mixed with quinoxaline prepared from authentic material.

Chlorination of 4,4′-dichlorostilbene. Chlorine was passed through a solution of 1.0 g. of 4,4′-dichlorostilbene (7) in 60 ml. of carbon tetrachloride at room temperature for one hour. Crystals began to separate from solution after a half hour. At the end of the reaction period the crystalline material was collected and dried in a vacuum. A yield of 0.55 g. of product was obtained which melted at 217–219°. After recrystallization from acetic acid the melting point was 227–228°. No depression of melting point could be detected when this material was mixed with the rearrangement product of I.

Hydrolysis of this synthetic *meso*-α,α′,4,4′-tetrachlorobibenzyl with alcoholic potassium hydroxide yielded *cis*-α,4,4′-trichlorostilbene, m.p. 59–60°. No depression of melting point could be observed when this material was mixed with similar material obtained from the hydrolysis of the product from the rearrangement of I.

The mother liquor from the chlorination procedure was evaporated at room temperature to a volume of about 2 ml. A second crop of *meso*-α,α′,4,4′-tetrachlorobibenzyl was removed by filtration. The filtrate was evaporated to dryness, and the residue recrystallized from alcohol, yielded prisms which melted at 95–96°.

Isomerization of dl-α,α′,4,4′-tetrachlorobibenzyl with anhydrous ferric chloride. An intimate mixture of 0.1 g. of *dl*-α,α′,4,4′-tetrachlorobibenzyl (m.p. 95–96°) with 1–2 mg. of anhydrous ferric chloride was heated in a bath at 110°. The product melted and then immediately set solid. Heating was discontinued after five minutes. The product melted at 227–228° after repeated recrystallizations from acetic acid, and showed no depression of melting point when mixed with *meso*-α,α′,4,4′-tetrachlorobibenzyl.

Isomerization of dl-dichlorostilbene with anhydrous ferric chloride. An intimate mixture of 0.3 g. of *dl*-dichlorostilbene (8) with 1–2 mg. of anhydrous ferric chloride was placed in an oil-bath at 105–115°. The material melted and then set solid during the course of ten minutes' heating. The product, recrystallized from alcohol, decomposed at 167°. When recrystallized from acetic acid it melted at 193–194°. No depression of melting point could be observed when the product was mixed with *meso*-dichlorostilbene (8). When the experiment was repeated without the addition of anhydrous ferric chloride, only *dl*-dichlorostilbene could be isolated from the heated material.

The carbon and hydrogen determinations were made by W. F. Barthel and S. B. Soloway.

SUMMARY

Anhydrous ferric chloride has been shown to rearrange catalytically 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane into *meso*-α,α′,4,4′-tetrachlorobibenzyl.

The latter compound was dehydrochlorinated by alcoholic caustic and also by heat to give two isomeric α,4,4′-trichlorostilbenes. Both these compounds were oxidized to 4,4′-dichlorobenzil and converted into the same quinoxaline derivative.

meso-α,α',4,4′-Tetrachlorobibenzyl and *dl*-α,α',4,4′-tetrachlorobibenzyl have been prepared by the chlorination of 4,4′-dichlorostilbene.

Anhydrous ferric chloride has been shown to catalyze the rearrangement of *dl*-α,α',4,4′-tetrachlorobibenzyl and *dl*-dichlorostilbene into the corresponding *meso*-isomers.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF INTERCHEMICAL CORPORATION]

THE DIENE ADDITION OF MALEIC ANHYDRIDE TO SORBIC ACID

ZENO W. WICKS, OLIVE W. DALY, AND HELEN LACK

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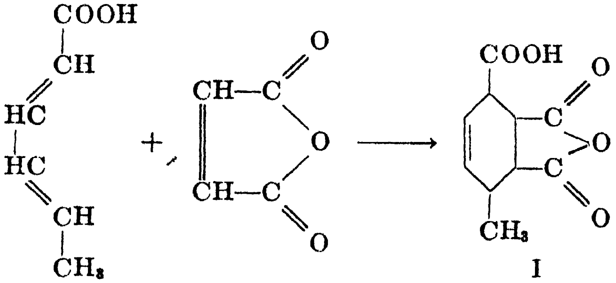
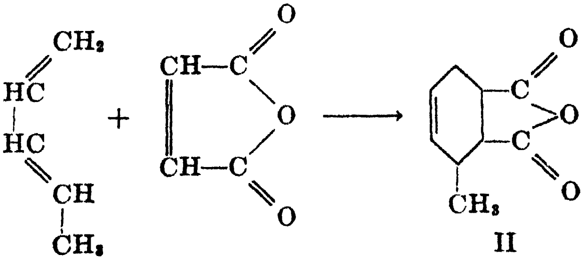
In attempting to prepare the maleic anhydride adduct of sorbic acid by simple fusion of the reactants as originally described by Diels and Alder (1), difficulty was experienced in obtaining the desired compound, I. The reaction was therefore investigated further in order to determine suitable conditions for the preparation and the cause for the failure of the first attempts.



I

Diels and Alder carried out the reaction on a ten-gram scale, heating the reactants until a vigorous reaction occurred, and obtained a viscous liquid as a product. They isolated the solid tribasic acid derived from I by hydrolysis of this liquid. On a rather larger scale, the present authors found that the reaction could be initiated by warming to 60° when a vigorous reaction ensued and the temperature rose spontaneously to 240–250° with considerable evolution of gas. No solid could be obtained, however, from the liquid product even by hydrolysis. It was found possible to repeat the results of Diels and Alder if the temperature was kept below 130°, for example, by adding the sorbic acid slowly to the molten maleic anhydride. It seems possible that, on the small scale in which Diels and Alder carried out the reaction, the temperature rise was not as great as that encountered in the present work.

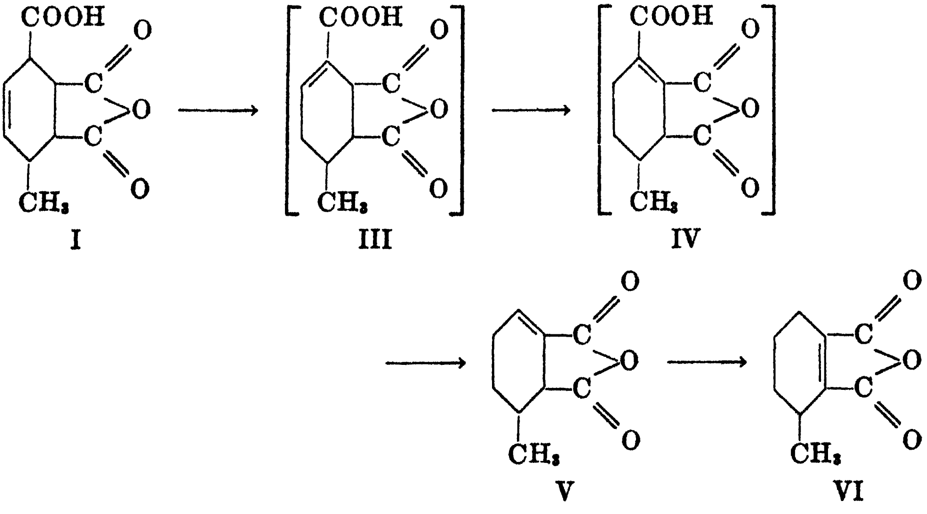
The product from the high temperature reaction was subjected to vacuum distillation. The major part of the material was found to be a liquid having the boiling point 117–118° at 2 mm. This is above that of the starting materials but substantially below any anticipated boiling point of the 6-carboxy-3-methyl-1,2,3,6-tetrahydrophthalic anhydride (I). A carbon and hydrogen analysis and



II

the saponification value of the distillate conformed to a decarboxylation product of I. For purposes of comparison, 3-methyl-1,2,3,6-tetrahydrophthalic anhydride (II), was prepared from piperylene and maleic anhydride (2). This substance had essentially the same boiling point (119° at 2 mm.) as that obtained from the reaction of maleic anhydride with sorbic acid at elevated temperatures, but in contrast to the other it readily solidified. It therefore appeared that the products were isomeric. This isomerism was confirmed by dehydrogenation of the decarboxylated product to give 3-methylphthalic anhydride.

The decarboxylation is unlikely to proceed prior to the addition reaction, since sorbic acid does not lose carbon dioxide when heated to 250° without catalysts. The direct adduct (I), was prepared by the procedure of Farmer and Warren (3), by heating a benzene solution of maleic anhydride and sorbic acid on a steam-bath. When I was heated to 150–160°, it underwent exothermic decarboxylation, yielding a liquid having the same properties as the decarboxylation product obtained directly from sorbic acid and maleic anhydride. Since a compound of structure I would not be expected to undergo decarboxylation easily, it may be postulated that the double bond of I shifts to the 5,6-position (IV).



Compound IV, being a cyclic analog of aconitic acid, would be expected to lose carbon dioxide readily. The product would have structure V, or by further isomerization part or all might be converted to VI. These isomers have conjugated double bonds, in contrast to the piperylene-maleic anhydride adduct (II).

This difference should be apparent in the optical properties of the isomers; therefore, the molecular refractivities and ultraviolet absorptions were compared.[1] For example II (super-cooled) showed no exaltation of molecular refraction ($M_{calc'd}$ 40.57; $M_{obs.}$ 40.36) while the decarboxylation products exhibited exaltation ($M_{calc'd}$ 40.57; M_{obs}, 41.63). Furthermore, the absorption of ultraviolet light by II was much less than the absorptions of the decarboxylated products, as can be seen in Figure 1. A further distinction between the conjugated

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[1] The authors wish to express their appreciation to Daniel Smith and Shirley Erhardt for the optical measurements involved in the determinations of absorption characteristics and exaltations.

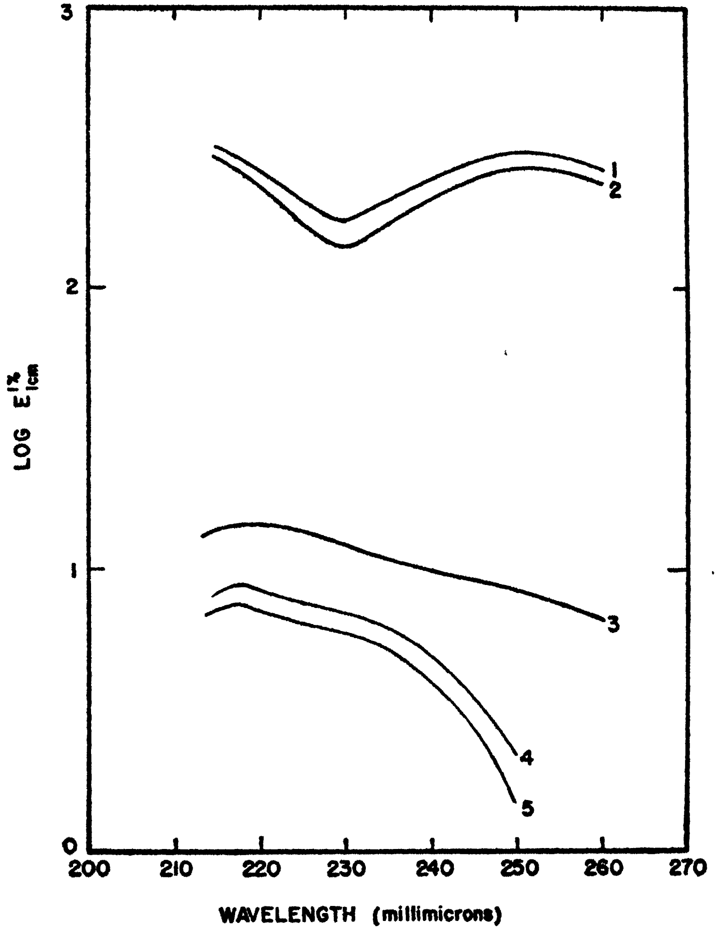

Fig. 1—Ultraviolet absorption spectra of alcoholic solution of:

(1) product of reaction of sorbic acid and maleic anhydride at elevated temperature.
(2) decarboxylation product from 6-carboxy-3-methyl-1,2.3 6-tetrahydrophthalic anhydride.
(3) 6-carboxy-3-methyl-1,2,3,6-tetrahydrophthalic anhydride.
(4) 3-methyl-1,2,3,6-tetrahydrophthalic anhydride after attempted isomerization by heating.
(5) 3-methyl-1,2,3,6-tetrahydrophthalic anhydride.

and non-conjugated isomers lay in their different rates of saponification. The first was readily saponified, less than half an hour heating with alcoholic alkali giving theoretical saponification values, while the second was only slowly saponified, several hours being required to complete saponification. This observation conforms to the previously reported greater reactivity of maleic anhydride as compared with succinic anhydride (4).

The preceding data point to the conclusion that the reaction product of maleic anhydride with sorbic acid at elevated temperatures is a conjugated isomer or isomers of 3-methyltetrahydrophthalic anhydride. On the basis of partial oxidation, Farmer and Warren (3) suggest that the product obtained from the addition of maleic anhydride to sorbic acid in benzene has structure III. In view of its low absorption of ultraviolet light as compared to that of the conjugated decarboxylation products as shown in Figure 1, curve 3, it seems more likely that the adduct has the unisomerized structure I. On the other hand, I must isomerize to III and IV quite readily in view of its easy decarboxylation. That the isomerization occurs before loss of carbon dioxide was shown by the failure of II to undergo conjugation during four hours heating at 230–260°, as compared with the fifteen minutes at 160–190° sufficient to isomerize and decarboxylate I. The ultraviolet absorptions of heated and unheated II are shown by curves 4 and 5 of Fig. 1. An attempt to convert the non-conjugated structure of II to its conjugated isomer by heating with alkali in ethylene glycol at 180–190° was also unsuccessful.

EXPERIMENTAL

Uncontrolled reaction of sorbic acid with maleic anhydride. A mixture of 448 g. of sorbic acid and 392 g. of maleic anhydride was heated slowly to 55° under an atmosphere of carbon dioxide to prevent oxidation. When the maleic anhydride melted, a slight evolution of gas was noted and then a vigorous reaction ensued. Even though the heater was removed, the temperature rose to 240–250° within five minutes and some material was lost through the condenser. The reaction product was allowed to cool and was found to be a somewhat viscous, brownish liquid from which no solid material could be obtained even by hydrolysis of a portion with water (1). The main portion of the product was subjected to vacuum distillation at 4 mm. There was a slight forerun, and then the main portion of the material distilled at 130–132°. There was an appreciable residue of polymeric (?) material from which no pure compound could be isolated. The main fraction was redistilled at 2 mm. pressure through a short Vigreux column; almost all of the material distilled at 117–118°. It has not been possible to make the product crystallize. It has the following properties: n_D^{25} 1.4969; d_4^{25} 1.1669; M_D: (calc'd) 40.57 (found) 41.63; for ultraviolet absorption characteristics see curve 1, Figure 1.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.05; H, 6.06; Sap. equiv. 83.1.
Found: C, 64.55, H, 6.07; Sap. equiv. 82.6.

The product was dehydrogenated by heating with 5% of a 5% palladium on charcoal at 250° for six hours. After distillation and recrystallization from benzene-petroleum ether, the product melted at 113–115°. Newman and McCleary (2) report the melting point of 3-methylphthalic anhydride as 114–115°.

Controlled reaction of sorbic acid with maleic anhydride. In order to moderate the reaction, 98 g. of maleic anhydride was heated to 100°, and while stirring, 112 g. of sorbic acid was added in small portions such that the temperature did not rise above 130°. The product after cooling was a viscous, resinous liquid. This material was refluxed with an equal weight of water for three hours and cooled. A pale yellow solid was obtained, yield 122 g. or 54%. The melting point was 198–205° with foaming, when heated rapidly; after several recrystallizations from water it was 224–230° with foaming. The neutral equivalent, 73.1, conforms to 6-carboxy-3-methyltetrahydrophthalic acid. Diels and Alder (1) report the melting point as 198° (decomp.).

6-Carboxy-3-methyl-1,2,3,6-tetrahydrophthalic anhydride, I. The preparation was carried out according to the directions of Farmer and Warren (3). The product was obtained in 64% yield and had the melting point 178°. For ultraviolet absorption characteristics see curve 3 of Fig. 1.

3-Methyl-1,2,3,6-tetrahydrophthalic anhydride II. In order to avoid the necessity for a long reaction time at low temperature (2), 102 g. of distilled piperylene and 197 g. of maleic anhydride, with a trace of Age-Rite Resin D[2] as a polymerization inhibitor, were heated in a hydrogenation bomb at 100° for two hours. The product was purified by distillation through a short column at 1.5 mm. pressure, and was obtained as a low-melting solid boiling at 116–118°. After further purification by redistillation, b.p. 119° at 2 mm., yield, 79%, the following properties were determined on the supercooled liquid: n_D^{25} 1.4932; d_4^{25} 1.1966, M_D: (calc'd) 40.57, (found) 40.36; for ultraviolet absorption characteristics see curve 5 of Figure 1.

Decarboxylation of 6-carboxy-3-methyl-1,2,3,6-tetrahydrophthalic anhydride. Twenty g. of the adduct (I) was heated under reflux to 160°; when this temperature was reached evolution of gas began. Without additional external heat the temperature rose to 190°. The gas evolved was shown to be carbon dioxide by testing with barium hydroxide solution. The product distilled at 121–122° at 2.5 mm., n_D^{25} 1.4968; d_4^{25} 1.1666; M_D: (calc'd) 40.57, (found) 41.66. These properties are essentially identical with those of the product from the reaction of maleic anhydride with sorbic acid at elevated temperatures. The ultraviolet absorption characteristics of the two materials are also very similar as can be seen in curves 1 and 2 of Figure 1.

SUMMARY

Preparation of the direct adduct of sorbic acid and maleic anhydride by simple fusion of the reactants is successful only if the temperature is kept below 150°. 6-Carboxy-3-methyl-1,2,3,6-tetrahydrophthalic anhydride is most readily prepared by carrying out the reaction of sorbic acid and maleic anhydride in benzene solution (3). If the temperature of the fusion reaction is allowed to rise over 150° or if the isolated adduct is heated to over 150°, rapid decarboxylation occurs leading to the formation of a conjugated isomer or isomers of 3-methyltetrahydrophthalic anhydride.

NEW YORK, N. Y.

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(1) DIELS AND ADLER, *Ann.*, **470**, 62 (1929).

(2) NEWMAN AND MCCLEARY, *J. Am. Chem. Soc.*, **63**, 1542 (1941).

(3) FARMER AND WARREN, *J. Chem. Soc.*, 897 (1929).

(4) REVETT AND SEDGWICK, *J. Chem. Soc.*, **97**, 1678 (1910).

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[2] Age-Rite Resin D can be obtained from R. T. Vanderbilt Co.

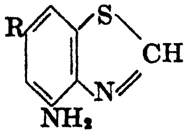
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

BENZOTHIAZOLES. II. NUCLEAR CHLORINATION IN THE HERZ PROCESS[1]

A. T. BLOMQUIST AND LINCOLN I. DIUGUID[2]

Received April 23, 1947

An investigation of the pharmacological properties of certain benzothiazole derivatives required, as intermediates for syntheses, a number of 4-aminobenzothiazoles variously substituted in the 6-position (I).

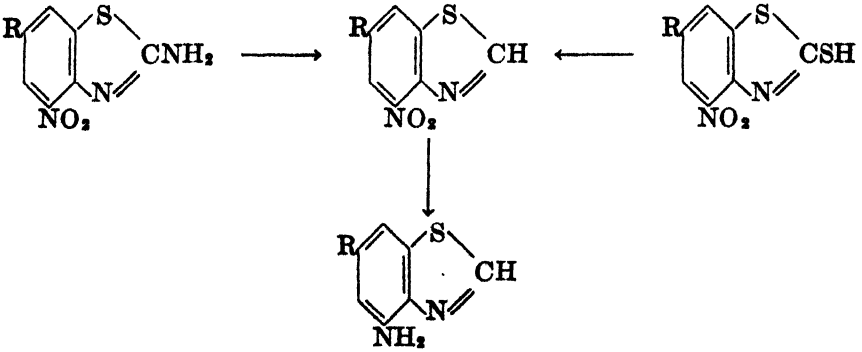


R = H, CH_3, Cl, CH_3O, CN

I

Benzothiazoles of this type (I) must be prepared indirectly through application of various cyclization procedures to *ortho*-substituted anilines and related compounds, as substitution methods cannot be used for the direct introduction of a group into the 4-position of the benzothiazole nucleus.

The more generally useful benzothiazole syntheses lead to 2-substituted derivatives such as 2-amino- and 2-mercapto-benzothiazoles. Accordingly, some attention was given to the replacement by hydrogen of substituents occupying the 2-position, with the object of achieving a convenient procedure for synthesizing 6-substituted-4-aminobenzothiazoles.



This proposed route to benzothiazoles of type I proved to be of limited value, for it was observed that (a) either the cyclization of a particular benzene derivative to the 2-amino- or 2-mercapto-benzothiazole went poorly or not at all, or

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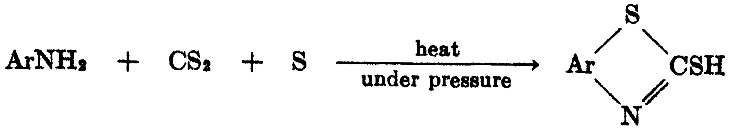
[1] This paper is an abstract of part of the doctoral dissertation of Lincoln I. Diuguid submitted to the Graduate Faculty of Cornell University in June, 1945.

[2] Wm. S. Merrell Co. Fellow in Chemistry, 1943–1945.

(b) subsequent replacement of the 2-amino or 2-mercapto group by hydrogen was difficult.

Although several 2-mercaptobenzothiazoles were obtained conveniently through the Sebrell and Boord synthesis (1) from primary aromatic amines, it

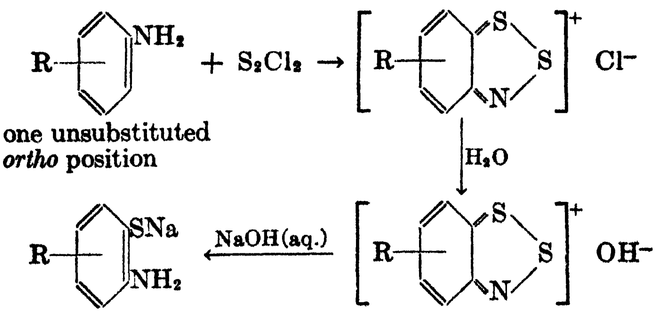


was observed that with certain aniline derviatives, *e.g.* 3-nitro-4-aminotoluene and 3-nitro-4-aminoanisole, the method failed when preparations were attempted on a scale larger than 0.1 mole. The replacement of the 2-mercapto group by hydrogen using iron and acetic acid succeeded with 2-mercapto-6-methylbenzothiazole, but failed with 2-mercapto-4-nitro-6-methyl- and 2-mercapto-4-nitro-6-methoxy-benzothiazoles.

The route to 6-substituted-4-aminobenzothiazoles through the corresponding 2-amino derivatives proved to be even less satisfactory. Both the procedure described in "Organic Syntheses" (2) and the method of Kaufmann (3) proved to be rather limited in scope. Thus, while the Kaufmann procedure gave good yields of 2-amino-4-nitro- and 2-amino-4-nitro-6-methyl-benzothiazole, it failed when applied to the cyclization of 3-nitro-4-aminobenzonitrile. Further, replacement of the 2-amino group by hydrogen could not be effected smoothly. Diazotization of the 2-amino derivatives and replacement of the diazonium salt group with hydrogen, using a number of reagents, did not work well. Only with 2-amino-4-benzamidobenzothiazole was there success in effecting a smooth conversion to 4-benzamidobenzothiazole by reduction of 2-chloro-4-benzamidobenzothiazole with red phosphorus and hydrogen iodide.

Because of the difficulties encountered with the 2-amino- and 2-mercapto-benzothiazole derivatives, attention was given to the Herz process which had been used successfully by Bogert (4) in the synthesis of 4-amino-6-methoxybenzothiazole.

The oroginal Herz process for the synthesis of *o*-aminothiophenols (5) involves the interaction of primary aromatic amines, their salts, or N-acetyl derivatives with sulfur monochloride either in the presence or absence of an unreactive diluent such as benzene, nitrobenzene, acetic acid, etc.



In a normal reaction the resulting chlorides formulated above are readily hydrolyzed to insoluble bases which on treatment with aqueous alkali afford *o*-aminothiophenols.

In the original patents Herz indicated that there was a strong tendency for nuclear chlorination to occur during the first step of the synthesis, particularly in the position *para* to the amino group. Further, this tendency is so marked that replacement by chlorine may even occur when the *para* position is occupied by $-NO_2$, $-CO_2H$, or $-SO_2$-groups.

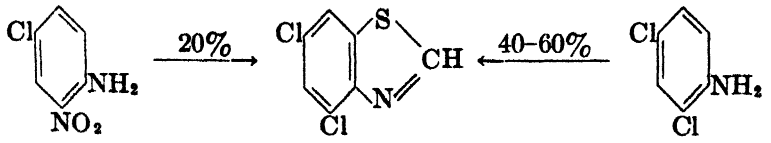
Subsequently, certain of these observations have been confirmed by other investigators in applying the Herz process to the synthesis of benzothiazoles. Thus, König (6) observed nuclear chlorination in the preparation of certain 2-methylbenzothiazoles. The Herz products derived from aniline and *o*-toluidine gave respectively 2-methyl-6-chloro- and 2,4-dimethyl-6-chloro-benzothiazole upon alkaline hydrolysis and treatment with acetic anhydride. Also with *p*-anisidine he observed the formation of a small amount of a chlorinated benzothiazole as an accessory product in the synthesis of 2-methyl-6-methoxybenzothiazole. It was suggested that this benzothiazole probably contained chlorine in the 5-position, although the positions 4 and 7 were not excluded.

Similarly Hixson and Cauwenberg (7) found that the Herz condensation product derived from *o*-amino-*p*-cymene contained chlorine in the position *para* to the amino group, as the same product was obtained on treatment of 2-amino-5-chloro-*p*-cymene with sulfur monochloride.

Finally, Ast and Bogert (8) noted that the condensation of *m*-nitrobenzoyl chloride with the *o*-aminothiophenol obtained by applying the Herz reaction to *p*-anisidine hydrochloride gave, in addition to the expected 2-(*m*-nitrophenyl)-6-methoxybenzothiazole, a small amount of a chlorinated benzothiazole of undetermined structure.

An investigation in our laboratory of the Herz process for benzothiazole syntheses has disclosed further abnormalities in the reaction. In these studies Bogert's excellent procedure for the conversion of 3-nitro-4-aminoanisole to 4-nitro-6-methoxybenzothiazole (4) was selected as a suitable standard procedure for evaluating the behavior of various substituted anilines in the Herz process.

Under these conditions it was observed that the crude Herz product derived from 2-nitro-4-chloroaniline did not afford the expected 4-nitro-6-chlorobenzothiazole when hydrolyzed with alkali and condensed with acetic-formic anhydride. The product, obtained, in about 20% yield, proved to be 4,6-dichlorobenzothiazole (m.p. 141.5–142.5°), for it was identical with the benzothiazole obtained from the Herz product derived from 2,4-dichloroaniline (40–60% yields).



It was also observed that both *o*-nitroaniline and *o*-chloroaniline afforded only 4,6-dichlorobenzothiazole when their crude Herz condensation products were treated with acetic-formic anhydride.

Thus it appears that the original remarks of Herz concerning the tendency for nuclear chlorination to occur in treating aromatic primary amines with sulfur monochloride may be extended to include the position *ortho* to the amino group as well as the *para* position.

The application of the Herz process to 3-nitro-4-aminotoluene and 3-nitro-4-aminobenzonitrile in an attempt to prepare 4-nitro-6-methylbenzothiazole and 4 nitro-6-cyanobenzothiazole did not prove useful. These amines on treatment with sulfur monochloride gave products which could not be hydrolyzed by water and the solutions obtained on alkaline hydrolysis gave no benzothiazole derivatives when treated in the usual way with acetic-formic anhydride.

The 4,6-dichlorobenzothiazole obtained from the several aniline derivatives was used as a starting material for the preparation of 4,6-dichloro-7-(β-diethylaminoethyl)aminobenzothiazole. 4,6-Dichlorobenzothiazole was readily nitrated by 98% nitric acid in the presence of concentrated sulfuric acid to yield 7-nitro-4,6-dichlorobenzothiazole. Reduction of this nitrobenzothiazole with iron and hydrochloric acid afforded 7-amino-4,6-dichlorobenzothiazole (m.p. 164–165°) in good yield. Alkylation of the aminobenzothiazole using the hydrobromide of β-diethylaminoethyl bromide proceeded smoothly upon heating in anhydrous *n*-butyl alcohol.

EXPERIMENTAL[3]

Preparation of Substituted 2-Mercaptobenzothiazoles

2-Mercapto-6-methylbenzothiazole, m.p. 175.5–178.5°, was prepared as described by Sebrell and Boord (1).

2-Mercapto-4-nitro-6-methylbenzothiazole, prepared similarly, was obtained in 30–65% yield in 0.1-mole runs; m.p. 258–259.5° from alcohol.

Anal. Calc'd for $C_8H_6N_2O_2S_2$: N, 12.39. Found: N, 12.49, 12.46.

2-Mercapto-4-nitro-6-methoxybenzothiazole was also obtained by the Sebrell and Boord procedure. In a typical preparation, on a 0.1-mole scale, 54% of the 2-mercaptobenzothiazole was obtained: unmelted at 360° on the Maquenne block.

Anal. Calc'd for $C_8H_6N_2O_3S_2$: N, 11 57. Found: N, 11.43, 11.58.

Preparation of 2-mercapto-4-nitro-6-methyl- (and 6-methoxy)-benzothiazole on a scale larger than 0.1 mole failed, as extensive decomposition always occurred.

Preparation of Substituted 2-Aminobenzothiazoles

2-Amino-4-nitrobenzothiazole was obtained in a highly impure state and in low yield by the method described in Organic Syntheses (2). Preparation by the method of Kaufmann (3) proved to be much more satisfactory and is described. To a solution of 30 g. (0.22 mole) of *o*-nitroaniline in 200 g. of 95% acetic acid contained in a 1-liter flask was added 40 g. of ammonium thiocyanate. A mixture of 40 g. of bromine in 60 cc. of glacial acetic acid was then added dropwise with stirring over a period of 1.75 hours. The mixture was allowed to stand 12 hours after the addition was complete. The reaction mixture was warmed on a water-bath, diluted with 400 cc. of hot water, and filtered. An excess of saturated sodium carbonate solution was added to the cooled orange colored filtrate, precipitating the crude 2-amino-4-nitrobenzothiazole as a yellow solid. After recrystallization from alcohol there was obtained 30 g. (70%) of the aminobenzothiazole, m.p. 110–112°. After purification through the acetyl derivative it melted at 130°. This compound has been reported by Dyson, Hunter, and Morris (9) as melting at 232°.

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[3] **All melting points recorded are uncorrected unless otherwise specified.**

Anal. Calc'd for $C_7H_5N_3O_2S$: N, 21.54. Found: N, 21.17, 21.33.

N-Acetyl derivative, m.p. 138–139°

Anal. Calc'd for $C_9H_7N_3O_3S$: C, 45.57; H, 2.95; N, 17.72.
Found: C, 45.28, 45.56; H, 3.20, 3.05; N, 17.87, 18.90.

2-Amino-6-methyl-4-nitrobenzothiazole. This aminobenzothiazole was prepared by the Kaufmann method outlined above. From 40 g. of 3-nitro-4-aminotoluene there was obtained 30 g. of a crude product which was contaminated with considerable amounts of thiocyanogen polymer; m.p. 110–220°. Extensive purification by recrystallization and sublimation in a vacuum gave a product satisfactory for analysis, m.p. 256–261°d.

Anal. Calc'd for $C_8H_7N_3O_2S$: N, 20.09. Found: N, 19.81, 19.71.

3-Nitro-4-aminobenzonitrile failed to give 2-amino-6-cyano-4-nitrobenzothiazole when subjected to the Kaufmann procedure outlined above. Most of the starting material was recovered unchanged together with a small amount of resinous material.

2-Amino-4-benzamidobenzothiazole. Using the method of Organic Syntheses (2), 40 g. of the monobenzoyl derivative of *o*-phenylenediamine, prepared according to Witt (10), afforded 23 g. (47%) of the desired 2-amino-4-benzamidobenzothiazole, m.p. 291–293° (on the Maquenne block).

Anal. Calc'd for $C_{14}H_{11}N_3OS$: N, 15.56. Found: N, 14.82, 15.03.

Preparation of Substituted 2-Chlorobenzothiazoles

2-Chloro-4-nitrobenzothiazole. Diazotization of 2-amino-4-nitrobenzothiazole followed by replacement of the diazonium salt group with chlorine proved to be the most satisfactory method for preparing 2-chloro-4-nitrobenzothiazole. To a solution of 10 g. of 2-amino-4-nitrobenzothiazole in 35 cc. of concentrated hydrochloric acid cooled to 0° was added with stirring a cold solution of 4.6 g. of sodium nitrite in 10 cc. of water over a period of 10–15 minutes. The solution of the diazonium salt was added with stirring to a solution of 5 g. of cuprous chloride in 40 cc. of concentrated hydrochloric acid at 0°. After the mixture had come to room temperature, it was steam distilled. From 2 l. of distillate was obtained 1.5 g. of crude product, which after several recrystallizations from methanol gave 1 g. of 2-chloro-4-nitrobenzothiazole, m.p. 59.5–61.5°.

Anal. Calc'd for $C_7H_3ClN_2O_2S$: N, 13.08. Found: N, 12.83, 12.96.

The preparation of 2-chloro-4-nitrobenzothiazole by (a) the action of sulfur monochloride on 2-mercapto-4-nitrobenzothiazole (11) or (b) the interaction of *o*-nitrophenylisothiocyanate and phosphorus pentachloride (12) proved to be unsatisfactory. Only viscous, tarry products, which could not be distilled at reduced pressure, were obtained.

2-Chloro-4-benzamidobenzothiazole. This substance was obtained by the diazotization and replacement procedure described above. From 24 g. of 2-amino-4-benzamidobenzothiazole there was obtained 13.5 g. (52%) of the desired 2-chloro derivative, m.p. 304° on the Maquenne block.

2-Chloro-6-methylbenzothiazole. Diazotization of 2-amino-6-methylbenzothiazole (2) followed by treatment with cuprous chloride-hydrochloric acid afforded the desired 2-chloro derivative in 8% yield, m.p. 48–49°.

Conversion of 2-Substituted Benzothiazoles to Benzothiazoles Unsubstituted in the 2-Position

4-Benzamidobenzothiazole. A mixture of 6.5 g. of 2-chloro-4-benzamidobenzothiazole, 2 g. of potassium iodide, 6 g. of red phosphorus, 70 cc. of orthophosphoric acid (85%), and 10 cc. of water was heated under reflux for 6 hours. The cooled reaction mixture was made alkaline with dilute sodium hydroxide, filtered, and the solid material washed with a little sodium bisulfite solution and with water. The crude product was then crystallized from alcohol, and yielded 4.4 g. (83%) of the desired 4-benzamidobenzothiazole, m.p. 287° on the Maquenne block.

Anal. Calc'd for $C_{14}H_{10}N_2OS$: N, 11.02. Found: N, 11.08, 11.07.

Since other 2-chlorobenzothiazoles were obtained with such great difficulty and in low yield through the Sandmeyer reaction on the 2-aminobenzothiazoles they were not studied in the reductive procedure given above.

Conversion of 2-amino-4-benzamidobenzothiazole to 4-benzamidobenzothiazole through the reduction of its diazonium salts by various standard procedures was not successful.

All attempts to hydrolyze 4-benzamidobenzothiazole with the object of obtaining 4-aminobenzothiazole failed. Treatment of the benzoyl derivative with boiling 25% sulfuric acid, 25% alcoholic potassium hydroxide, and 100% phosphoric acid were without effect.

6-Methylbenzothiazole. 2-Mercapto-6-methylbenzothiazole was used as a model compound for studying the replacement of the 2-mercapto group by hydrogen. A mixture of 10 g. of 2-mercapto-6-methylbenzothiazole, 100 cc. of 90% acetic acid, 25 cc. of ethyl alcohol, and 10 g. of iron powder was heated under reflux for 36 hours. During the period five 10-cc. portions of water were added at regular intervals. At the end of this time hydrogen sulfide evolution had ceased, and the reduction appeared to be complete. The cooled mixture was diluted with water to 500 cc. and extracted with benzene. The aqueous layer was neutralized with sodium carbonate and also extracted with benzene. The combined benzene extracts were dried and the benzene removed by distillation. The residue was then distilled under reduced pressure, and afforded 6.4 g. (82%) of pure 6-methylbenzothiazole, b.p. 118–120°/1.3 mm.; m.p. 15.5°; m.p. of picrate, 163.5°. These constants agree well with the values recorded in the literature for 6-methylbenzothiazole (13).

The reduction of 2-mercapto-4-nitro-6-methylbenzothiazole and 2-mercapto-4-nitro-6-methoxybenzothiazole by the method described above failed to give useful products. Other metal-acid combinations and low-pressure hydrogenation using a large excess of Raney nickel in Methyl Cellosolve and in dioxane also gave negative results.

Behavior of Some Substituted Anilines in the Herz Process

The procedure of Bogert and Fox (4) for the conversion of 3-nitro-4-aminoanisole to 4-nitro-6-methoxybenzothiazole was used as a standard procedure for evaluating the behavior of the aniline derivatives listed below in the Herz process.

2,4-Dichloroaniline gave an orange-red Herz condensation product which was converted smoothly into 4,6-dichlorobenzothiazole. From 32 g. of the aniline there was obtained 27 g. of crude product, m.p. 136–138°. Recrystallization from ethyl alcohol gave 21 g. (50%) of white needle-like crystals, m.p. 142–142.5°.

Anal. Calc'd for $C_7H_3Cl_2NS$: N, 6.86; Cl, 34.75.
Found: N, 6.73, 6.80; Cl, 34.64, 34.88.

o-Chloroaniline gave a crude Herz product which was not completely soluble in aqueous alkali. The filtered alkaline solution, when treated with acetic-formic anhydride, gave a crude benzothiazole which after recrystallization melted at 140–141°, 38% yield. A mixed melting point with the 4,6-dichlorobenzothiazole derived from 2,4-dichloroaniline showed no depression.

4-Chloro-2-nitroaniline gave a crude Herz product which was almost completely soluble in aqueous alkali. Treatment of the alkaline solution of the thiophenol with acetic-formic anhydride gave a light yellow precipitate which crystallized from alcohol in white needles, m.p. 141.5–142.5°, 20% yield. This substance showed no depression in melting point when mixed with 4,6-dichlorobenzothiazole.

o-Nitroaniline gave a crude Herz product which was resistant to alkaline hydrolysis, most of the material failing to go into solution. Treatment of the clear alkaline solution with the mixed anhydride gave, after recrystallization from alcohol, 1 g. (2.7%) of 4,6-dichlorobenzothiazole.

3-Nitro-4-aminotoluene (152 g.) gave a crude Herz product which was for the most part unaffected by aqueous alkali. The precipitate (19 g.) obtained on treatment of the clear alkaline solution with the mixed anhydride did not behave like a simple benzothiazole derivative. It was insoluble in all the common organic solvents and was not altered by metal-acid reducing agents. It was not investigated further.

p-Chloroaniline (25 g.) afforded a crude Herz product which, when treated with aqueous alkali, gave a dark blue solution depositing an orange-yellow oil after the addition of acetic-formic anhydride. The oil solidified slowly, and was then crystallized from alcohol, m.p. 185–205°. After three more recrystallizations of the crude product (21 g.) from alcohol the substance melted sharply at 212–214°.

Analytical and molecular weight data indicated that 6-chlorobenzothiazole was not at hand.

Anal. Calc'd for C_7H_4ClNS: N, 8.26; Cl, 20.93; Mol. wt., 169.5.

Found: N, 8.01, 7.82; Cl, 18.17, 18.25; Mol. wt. (Micro Rast), 458.

The product was not investigated further.

3-Nitro-4-aminobenzonitrile gave a crude Herz product which was insoluble in aqueous alkali. Treatment of the alkaline filtrate with acetic-formic anhydride gave no water-insoluble product.

Benzothiazoles Derived from 4,6-Dichlorobenzothiazole

7-Nitro-4,6-dichlorobenzothiazole. To 15 g. of 4,6-dichlorobenzothiazole dissolved in 25 cc. of concentrated sulfuric acid was added dropwise 25 cc. of 98% nitric acid, maintaining the temperature of the reaction mixture at 50°. After all the nitric acid had been added, the mixture was heated at 70° for ten minutes, and then poured onto ice. The solid precipitate was filtered, washed, and recrystallized from ethyl alcohol. There was obtained 16.5 g. (85%) of 7-nitro-4,6-dichlorobenzothiazole as light yellow crystals, m.p. 154–155°.

Anal. Calc'd for $C_7H_2Cl_2N_2O_2S$: N, 11.25. Found: N, 11.34, 11.32.

4,6-Dichloro-7-aminobenzothiazole. Reduction of 16.5 g. of 7-nitro-4,6-dichlorobenzothiazole with iron and hydrochloric acid gave 12 g. (85%) of 4,6-dichloro-7-aminobenzothiazole, m.p. 164–165°.

Anal. Calc'd for $C_7H_4Cl_2N_2S$: Cl, 32.39. Found: Cl, 32.37.

4,6-Dichloro-7-(β-diethylaminoethyl)aminobenzothiazole. A mixture of 10 g. of 4,6-dichloro-7-aminobenzothiazole, 10 g. of β-diethylaminoethyl bromide hydrobromide and 20 cc. of dry *n*-butyl alcohol was heated under reflux at 130–140° for 40 hours. The mixture was then poured into 100 cc. of water, made alkaline with excess sodium carbonate, and extracted with ether. The ether extract was dried over potassium carbonate, filtered, and distilled. The alkylated aminobenzothiazole (5 g.) was obtained as an amber-colored viscous liquid, b.p. 205–215°/0.1 mm.

Anal. Calc'd for $C_{13}H_{17}Cl_2N_3S$: N, 13.22. Found: N, 13.29, 13.15.

SUMMARY

1. The synthesis of certain 4,6-disubstituted benzothiazoles by several routes has been investigated. Such syntheses through the corresponding 2-mercapto and 2-amino derivatives have not proved to be generally useful.

2. The behavior in the Herz process of a number of substituted anilines has been studied. *o*-Nitroaniline, *o*-chloroaniline, and 2-nitro-4-chloroaniline undergo nuclear chlorination by substitution or replacement in the *ortho* and/or *para*

positions. *p*-Chloroaniline, 3-nitro-4-aminotoluene, and 3-nitro-4-aminobenzonitrile afford complex products not hydrolyzable to simple thiophenols.

3. A few benzothiazoles derived from 4,6-dichlorobenzothiazole are described.

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[CONTRIBUTION FROM THE INSTITUTO DE FISIOLOGÍA, FACULTAD DE CIENCIAS MÉDICAS]

BENZOYLATED NITRILES OF ALDONIC ACIDS. DEGRADATION ACCORDING TO WOHL AND ZEMPLÉN METHODS

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Received May 1, 1947

The degradation of acylated nitriles of aldonic acids, with ammonia, known in sugar chemistry as Wohl's method of degradation, has been usually applied to acetyl derivatives, with the exception of the work of Brigl, Mühlschlegel, and Schinle (1) who prepared hexabenzoyl mannoheptonic nitrile, and obtained by the action of silver nitrate in methanolic ammonia, mannose dibenzamide and mannose monobenzamide.

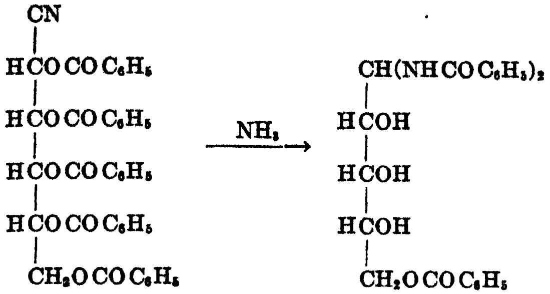
According to Brigl *et al.*, the dibenzamide is produced during the degradation, and the monobenzamide is a secondary product arising from the action of nitric acid, produced during working up the reaction products, on the dibenzamide already formed. The formation of a monoacylamide compound in the Wohl degradation can be viewed from another point after Hockett and Chandler (2) obtained glucose monoacetamide by the degradation of hexaacetyl-D-α-glucoheptonic nitrile without employing silver nitrate or oxide, but only ammonia, and Niemann and Hays (3) obtained the same compound by treating β-D-glucose pentaacetate with methanolic ammonia. It is evident that variations of the classical products obtained in the Wohl degradation can be expected with different aldonic acids, and that also some variation might result from employing acids with different acylating residues. Our work is related to this latter possibility.

We now describe the preparation of the benzoylated nitriles of the four aldonic acids derived from D-glucose, D-galactose, D-mannose, and L-rhamnose. They were easily prepared by the action of benzoyl chloride on the oximes of the sugars suspended in pyridine.

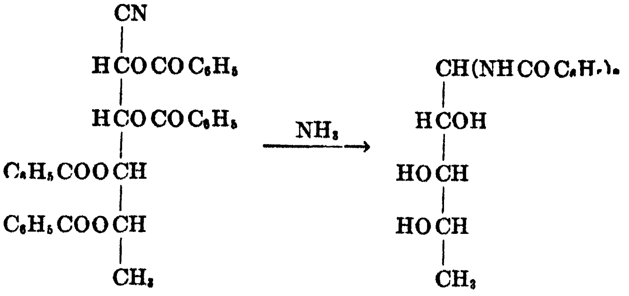
It was found that the nitriles can be degraded by treatment with 96% ethanol saturated with ammonia. They were left unattacked by lower concentrations of ammonia and by concentrated aqueous ammonia, in this last case seemingly because of their insolubility.

In all cases, the dibenzamides of the lower sugars were obtained in smaller yields than is usual with the acetylated nitriles. The dibenzamides obtained from pentabenzoyl-D-gluconic acid nitrile, pentabenzoyl-D-mannonic acid nitrile, and pentabenzoyl-D-galactonic acid nitrile, when analyzed, revealed the presence of three benzoyl residues, while from tetrabenzoyl-L-rhamnonic acid nitrile (I), 5-desoxy-L-arabinose dibenzamide (II) was obtained.

It is evident that in the case of the former nitriles, one of the esterifying benzoyl groups remains, and resists the action of the ammonia. Although we have not a direct proof, the difference in reaction between benzoylated nitriles with a primary alcoholic hydroxyl, and tetrabenzoyl-L-rhamnonic acid nitrile, where there is none, justifies the hypothesis that the remaining benzoyl is attached to the 5



Hexose series



(I) (II)

Desoxyhexose series

carbon atom in the pentoses produced, and that the products obtained by degradation are: 5-benzoyl-D-arabinose dibenzamide and 5-benzoyl-D-lyxose dibenzamide.

The preparation of some acetylated and benzoylated derivatives of the benzamides has confirmed their formulas.

This resistance of the primary benzoyl group to hydrolysis by alcoholic ammonia has been described also by Todd, who found that methanolic ammonia hydrolysis of 5-benzoyl-2,3,4-triacetyl-L-arabinose derivatives removes the acetyl groups, leaving the benzoyl group unaffected (4).

In the experiments of Brigl, Mülschlegen, and Schinle (1), all the benzoyl groups were removed, and only new experimental work can decide if this difference can be attributed to the silver salt used in the degradation, together with slightly different conditions.

When Zemplén's method of degradation with sodium methoxide was applied, all benzoyl groups were removed, and D-arabinose was isolated from pentabenzoyl-D-gluconic and pentabenzoyl-D-mannonic nitriles.

EXPERIMENTAL

Pentabenzoyl-D-galactonic acid nitrile. Five grams of D-galactose oxime, finely divided, was suspended in 30 ml. of pyridine and 28.2 ml. of benzoyl chloride slowly added. Heat developed and the oxime dissolved. After 24 hours the partly solidified mass was poured into water, and a sirup precipitated, which by washing many times with cold water solidified.

This solid was filtered, well dried, and recrystallized from acetic acid. Sixteen and two-tenths grams (98% yield) of pentabenzoyl-D-galactonic acid nitrile, melting at 142–144°, was obtained. Recrystallized many times from ethanol, long needles melting at 144° were obtained. It is very soluble in cold chloroform, ether, acetone, and benzene, sparingly soluble in cold methanol and ethanol, insoluble in petroleum ether and water. $[\alpha]_D^{20}$ in chloroform +9.7° (*c*, 1.33).

Anal. Calc'd for $C_{41}H_{31}NO_{10}$: C, 70.30; H, 4.44; N, 2.00.
Found: C, 70.15; H, 4.46; N, 2.31.

*5-Benzoyl-*D*-lyxose dibenzamide.* Three grams of pentabenzoyl-D-galactonic acid nitrile was suspended, finely divided, in 90 ml. of 96% ethanol saturated with ammonia, and shaken at room temperature. After 2 hours, the nitrile had dissolved, and shaking was continued for one hour. The solution was concentrated to dryness in a vacuum, and the dried residue washed well with cold ethanol until no more color was removed. The remaining 5-benzoyl-D-lyxose dibenzamide melted at 210–218° and could be purified by recrystallization from a large volume of ethanol; long needles melting at 222–224°; sparingly soluble in all common organic solvents except pyridine. $[\alpha]_D^{25}$ +36.1° in pyridine (*c*, 0.71).

Anal. Calc'd for $C_{26}H_{26}N_2O_7$: C, 65.27; H, 5.43.
Found: C, 65.77; H, 5.35.

*5-Benzoyl-2,3,4-triacetyl-*D*-lyxose dibenzamide.* 5-Benzoyl-D-lyxose dibenzamide (0.35 g.) was treated with 2.5 ml. of pyridine and 2.5 ml. of acetic anhydride and heated until all dissolved. After 24 hours, the solution was poured into ice-water, and a sirup precipitated that crystallized easily. The crystals (yield 0.42 g.) were recrystallized from ethanol; fine needles melting at 189°; $[\alpha]_D^{23}$ +36.2° in chloroform (*c*, 0.95).

Anal. Calc'd for $C_{32}H_{32}N_2O_{10}$: C, 63.57; H, 5.29.
Found: C, 63.10; H, 5.21.

*Tetrabenzoyl-*D*-lyxose dibenzamide.* 5-Benzoyl-D-lyxose dibenzamide (0.5 g.) was treated with 5 ml. of pyridine and 3.5 ml. of benzoyl chloride. The reaction mass after 24 hours was poured into ice-water and purified in the usual way. The crude product, recrystallized from acetic acid, gave needles melting at 227–229°. $[\alpha]_D^{19}$ +39.1° in chloroform (*c*, 0.88).

Anal. Calc'd for $C_{47}H_{38}N_2O_{10}$: C, 71.39; H, 4.81.
Found: C, 71.78; H, 5.74.

*Pentabenzoyl-*D*-gluconic acid nitrile.* Five grams of glucose oxime was suspended in 30 ml. of pyridine and treated with 28 cc. of benzoyl chloride. The semi-solid reaction product stood for 24 hours, and then was treated as described for pentabenzoyl-D-galactonic acid nitrile. From acetic acid it was obtained in prisms melting at 114–115°, yield 12 g., 71%. By recrystallization from acetic acid the melting point 118° was attained. It is very soluble in chloroform, ether, acetone, and benzene, less so in methanol and ethanol. $[\alpha]_D^{20}$ +15.1° in chloroform (*c*, 2.09).

Anal. Calc'd for $C_{41}H_{31}NO_{10}$: C, 70.30; H, 4.44.
Found: C, 70.31; H, 4.95.

*5-Benzoyl-*D*-arabinose dibenzamide.* Five grams of pentabenzoyl-D-gluconic acid nitrile, finely ground, was suspended in 150 ml. of ethanol saturated with ammonia, and shaken for 2.5 hours, when all the solid dissolved. The solution was then concentrated in a vacuum, the residue very well dried, and then washed with cold methanol. Nine-tenths gram of residue melting at 205–208° was obtained. This product, when dissolved in various organic solvents, precipitated on cooling as a gel-like solid. This property was not changed by many solutions and precipitations from methanol, and the product had the constant melting point 206–208°. An X-ray analysis, for which we are indebted to Ing. Galloni, showed that it has a crystalline structure. It has low solubility in cold methanol, ethanol, and ethyl acetate, but is more soluble at higher temperatures; almost insoluble in benzene and water, soluble in pyridine; $[\alpha]_D^{21}$ +8.5° in pyridine (*c*, 1.17).

Anal. Calc'd for $C_{26}H_{26}N_2O_7$: C, 65.27; H, 5.43.
Found: C, 64.90; H, 5.57.

*5-Benzoyl-2,3,4-triacetyl-*D*-arabinose dibenzamide.* 5-Benzoyl-D-arabinose dibenzamide (0.5 g.), melting at 205–207° was dissolved in 5 ml. of pyridine, and 5 ml. of acetic anhydride added. After 24 hours at room temperature, the solution was poured into ice-water. The precipitated sirup crystallized on washing, and recrystallized from methanol gave rhombic plates melting at 193°; $[\alpha]_D^{23}$ +69.0° in chloroform (*c*, 0.81).

Anal. Calc'd for $C_{32}H_{32}N_2O_{10}$: C, 63.57; H, 5.29.
Found: C, 63.83; H, 5.80.

5-Benzoyl-D-*arabinose dibenzamide from 5-benzoyl-2,3,4-triacetyl*-D-*arabinose dibenzamide.* A small amount of 5-benzoyl-2,3,4-triacetyl-D-arabinose dibenzamide was dissolved in an excess of ethanol saturated with ammonia, and shaken for three hours at room temperature. The solution was evaporated, and the well-dried residue washed with water and methanol; recrystallization from methanol gave a product melting at 207–208° which gave no depression when mixed with the original 5-benzoyl-D-arabinose dibenzamide. It maintained the property of giving gel-like precipitates when its solution in a hot organic solvent was cooled.

Pentabenzoyl-D-*mannonic acid nitrile.* One gram of finely-divided mannose oxime was suspended in 6 ml. of pyridine and 5.5 ml. of benzoyl chloride added slowly. After 24 hours at room temperature, the semi-solid mass was poured into ice-water. The precipitated sirup solidified slowly on washing with water. The solid was well dried and dissolved in the minimum amount of acetic acid with a little heating. After 24 hours, 3 g. (93%) of crystals melting at 120° was collected. By recrystallization from methanol or ethanol, plates melting at 130° were obtained, but large losses took place in the purification; soluble in chloroform, ether, acetone, and benzene, less so in methanol and ethanol; $[\alpha]_D^{17}$ +10.2° in chloroform (*c*, 1.37).

Anal. Calc'd for $C_{41}H_{31}NO_{10}$: C, 70.30; H, 4.44.
Found: C, 70.63; H, 4.70.

5-Benzoyl-D-*arabinose dibenzamide from pentabenzoyl*-D-*mannonic acid nitrile.* One gram of pentabenzoyl-D-mannonic acid nitrile was shaken for 3 hours with 30 ml. of ethanol saturated with ammonia. In the usual way, 0.1 g. (much less than from the gluconic acid nitrile) of residue melting at 200° was obtained. Recrystallization from methanol gave the m.p. 205–207°. The solid gave no depression in melting point when mixed with a sample of 5-benzoyl-D-arabinose dibenzamide from gluconic acid nitrile, and precipitated from its solutions in methanol in a gel-like condition.

Tetrabenzoyl-L-*rhamnonic acid nitrile.* Three grams of rhamnose oxime was dissolved at room temperature in 18 ml. of pyridine and treated with 16.5 ml of benzoyl chloride. After 24 hours, the semi-solid mass was poured into ice-water, and the sirup that precipitated solidified by washing. It was filtered, dried, and recrystallized from methanol, 9 g. (91% yield) of long prisms melting at 110°. By further recrystallization, the melting point 114° was obtained; very soluble in chloroform, ether, acetone, and benzene, much less so in methanol or ethanol, insoluble in water $[\alpha]_D^{21}$ +4.7° in chloroform (*c*, 1.14).

Anal. Calc'd for $C_{34}H_{27}NO_8$: C, 70.71; H, 4.68.
Found: C, 70.79; H, 4.77.

5-Dexosy-L-*arabinose dibenzamide.* Five grams of tetrabenzoyl-L-rhamnonic acid nitrile was suspended in 150 ml. of ethanol saturated with ammonia and shaken for two hours; all the solid had then dissolved. The solution was distilled in a vacuum, and the dried residue washed well with methanol. Four-tenths gram of 5-dexosy-L-arabinose dibenzamide was obtained, that recrystallized from acetic acid or methanol gave needles melting at 225–226°; very sparingly soluble in water and in all cold organic solvents except pyridine. $[\alpha]_D^{18}$ −2.1° in pyridine (*c*, 0.71).

Anal. Calc'd for $C_{19}H_{22}N_2O_5$: C, 63.18; H, 6.14.
Found: C, 62.85; H, 6.28.

Triacetyl-5-desoxy-L-*arabinose dibenzamide.* Five-tenths gram of the dibenzamide was treated with 5 ml. of pyridine and 5 ml. of acetic anhydride, and gently heated until the solid dissolved. After 24 hours at room temperature, the solution was poured into ice-water, and the precipitated sirup crystallized very easily. Recrystallized from chloroform-petroleum ether, rhombic plates melting at 193° were obtained. $[\alpha]_D^{19}$ −92.9° in chloroform (*c*, 0.92).

Anal. Calc'd for $C_{25}H_{28}N_2O_8$: C, 61.98; H, 5.78.
Found: C, 61.71; H, 5.66.

*Tribenzoyl-5-desoxy-*L*-arabinose dibenzamide.* The dibenzamide (0.15 g.) was treated with 0.9 ml. of pyridine and 0.8 ml. of benzoyl chloride. After 24 hours standing at room temperature, the crude benzoyl derivative was isolated in the usual way, and recrystallized from methanol; rhombic plates melting at 212°.

Anal. Calc'd for $C_{40}H_{34}N_2O_8$: C, 71.64; H, 5.07.
Found: C, 70.96; H, 5.33.

Degradations with Sodium Methoxide

*Pentabenzoyl-*D*-gluconic acid nitrile.* The nitrile (8.25 g.) was dissolved in 7 ml. of chloroform and cooled to −5°. A solution of 0.82 g. of sodium in 7 ml. of methanol was then added with vigorous shaking. A reddish gel-like mass was formed. After 5 minutes, 20 ml. of ice-water and 2 ml. of acetic acid were added, and the aqueous solution concentrated to dryness. The residue was treated with 20 ml. of absolute ethanol, the ethanol evaporated, and this operation repeated once. The residue gave a clear solution when dissolved to 26 ml. with water. From 13 ml. of this solution, 0.32 g. of D-arabinose diphenylhydrazone was isolated, melting at 202–204°; yield as arabinose, 31%.

*Pentabenzoyl-*D*-mannonic acid nitrile.* The nitrile (8.25 g.) was dissolved in 10 ml. of chloroform (a larger amount than in the previous degradation) and treated exactly as the gluconic nitrile. A yield of 18% of arabinose, isolated as diphenylhydrazone was obtained.

BUENOS AIRES, ARGENTINA

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[From the United States Department of Agriculture, Agricultural Research Administration, Bureau of Entomology and Plant Quarantine]

CORRECTION OF THE SOURCE OF "AFFININ" (N-ISOBUTYL-2,6,8-DECATRIENOAMIDE)

MARTIN JACOBSON, FRED ACREE, Jr., and H. L. HALLER

Received May 14, 1947

The isolation of an insecticidal amide from the roots of a Mexican plant submitted to the Bureau of Entomology and Plant Quarantine in 1943 and 1944 as *Erigeron affinis* DC. (common name "peritre del pais" or "chilcuan") and its identification as N-isobutyl-2,6,8-decatrienoamide have been reported in two previous papers (1, 2). The name "affinin" was proposed for this amide after several unsuccessful attempts were made to obtain an authentic botanical specimen for positive identification.

TABLE I

Comparison of Physical Constants and Toxicity to House Flies of "Affinin" and Distillate from *Heliopsis longipes*

SUBSTANCE	B.P. (0.3 mm.)	n_D^{27}	TOXICITY TO HOUSE FLIES		
			Concn. of plant	Knockdown in 10 min.	Mortality in 1 day
	°C		*Mg./ml.*	*Percent*	*Percent*
"Affinin"	160–162	1.5128	122.8	100	39
Pyrethrins standard (1 mg./ml.)				100	40*
Distillate from *H. longipes* roots	160–162	1.5125	122.8	100	21
Pyrethrins standard (2 mg./ml.)				100	13*

* Different broods of flies.

In 1946 Elbert L. Little, Jr., of the Foreign Economic Administration, called attention (unpublished report) to the confusion in the botanical classification of Mexican "peritre del pais" ("native pyrethrum") and pointed out that the plant was actually *Heliopsis longipes* (A. Gray) Blake (family *Compositae*), common name "chilcuague" or "chilcuan."

Recently authentic *Heliopsis longipes* roots, obtained from Mexico through the Office of Defense Supplies, Reconstruction Finance Corporation, were extracted with petroleum ether, and the extract was worked up by the nitromethane and charcoal procedure previously used to obtain "affinin" (1). Upon distillation of the nitromethane-soluble product, 0.56% (dry-root basis) of a pale-yellow oil was obtained, which crystallized in the cold. It was shown to be N-isobutyl-2,6,8-decatrienoamide by comparison of the physical constants and toxicity to house flies with these properties of "affinin" (Table I).[1] Further proof of its identity was obtained by hydrogenation of the oil, and by the isolation of isobutylamine and capric acid from the reaction mixture resulting from the hydrolysis of the hydrogenated oil.

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[1] The tests against house flies were made by W. A. Gersdorff of this Bureau.

It is proposed that the use of the name "affinin" for N-isobutyl-2,6,8-decatrienoamide obtained from this plant be discontinued.

SUMMARY

It has been shown that the botanical source of the insecticidal amide N-isobutyl-2,6,8-decatrienoamide is *Heliopsis longipes* (A. Gray) Blake instead of *Erigeron affinis* DC.

BELTSVILLE, MD.

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[Contribution No. 101 from the Research Laboratories of Hoffmann-La Roche, Inc.]

CRYSTALLINE 1-IODO-1-DESOXY-2,3; 4,6-DIISOPROPYLIDENE-L-SORBOSE

THOMAS S. GARDNER AND JOHN LEE

Received June 4, 1947

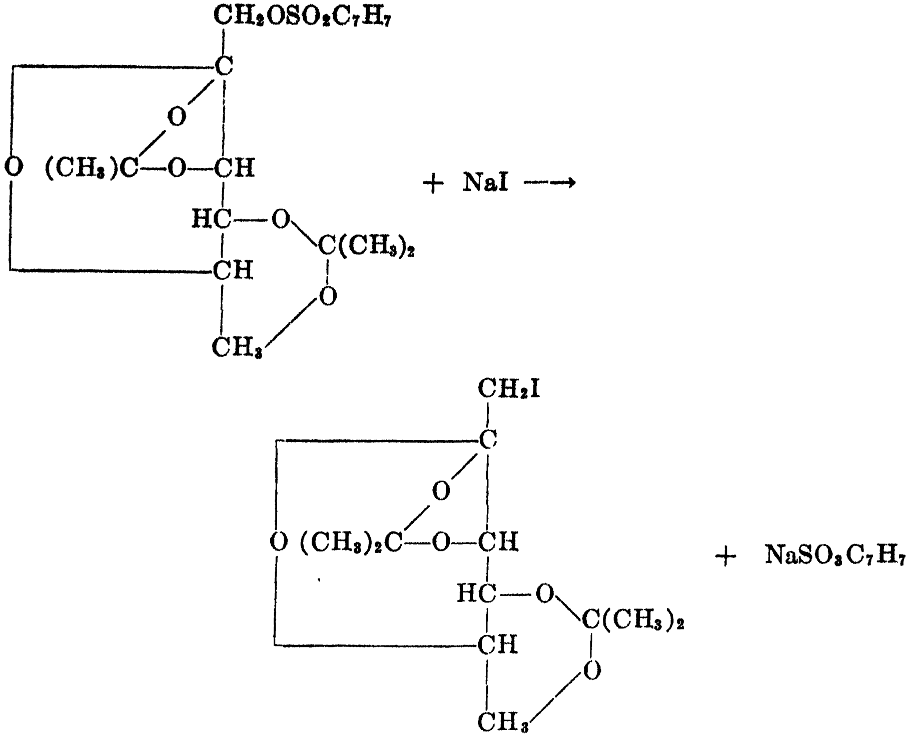
The substitution of tosyloxyl by iodine using sodium iodide in acetone (1) or acetonylacetone (2) has been used as a characterization test for primary alcoholic groups. This procedure has been based on the observation that tosyl esters on secondary alcoholic groups are not replaced under similar conditions (1).

An apparent anomaly occurs in the case of tosyl esters adjacent to a keto group. The general opinion was expressed in a recent review on this reaction (3) as follows: "A tosyloxyl group on the primary alcoholic carbon 1 of certain keto sugar derivatives is unreactive." Other investigators state that the reaction is either very slow or does not take place at all (4).

However, in a few cases the reaction has been shown to take place. A sirupy 1,6-diiodo-1,6-didesoxy-2,3-acetone-L-sorbose was prepared by the action of sodium iodide in acetone on the 1,6-ditosyl compound at 130° for five days (5). A crystalline 1-iodo-1-desoxy-2,3-monoacetone-D-fructomethylose was prepared at 125° for 48 hours from the 1-tosyl derivative with sodium iodide in acetone (6). A crystalline 1-iodo-1-desoxy-2,3-monoacetone-L-sorbomethylose was prepared at 125° for 36 hours with sodium iodide in acetone (5). An impure 1-iodo-1-desoxy-4-tosyl-monoacetone-D-xylulose was prepared as a sirup contaminated with the unchanged 1,4-ditosyl derivative at 100° for 8 hours (7). However, 1-tosyl-2,3; 4,5-diacetonefructose was found to undergo no change during 8 hours at 100° with sodium iodide in acetone (5, 7) and 3 days at 130° also failed to yield an iodo derivative (5).

From this it appears that in the methylose forms of fructose and sorbose the C_1 tosyloxy ester adjacent to a keto group may be replaced by the iodine group but the reaction is much slower than with a tosyloxy ester group removed from the keto group by at least one carbon. The difference in reaction between the two types of primary alcoholic groups is clearly demonstrated by work on the rate of tosylation (8) and tritylation (9) of 1,2;3,4-diacetone-D-galactose and 2,3;4,6-diacetone-L-sorbose. In each case the rate of reaction of the C_6 primary hydroxyl of the galactose derivative was several times faster than the C_1 primary alcoholic group of the sorbose derivative.

In this investigation we wish to report a study made on the preparation of crystalline 1-iodo-1-desoxy-2,3;4,6-diisopropylidene-L-sorbose (1-iodo-1-desoxy diacetonesorbose) from the corresponding 1-tosyloxy compound by the general reaction as follows:



This is the first report of this type of crystalline derivative from a carbohydrate of the general formula, *i.e.* $(CH_2O)_x$, in contrast to the methylose sugar derivatives cited above (5, 6). The 1-iodo-1-desoxy compound was prepared using sodium iodide in acetone at 100° for long periods of time in a step-wise iodination. It was found that on iodination in one step only 50–80% conversion was obtained at 100° for 100 hours. Iodination at 120° for 4 hours, using acetonylacetone as a solvent, gave the starting material apparently unchanged, while at 150° for 4 hours complete decomposition of the compound took place, with the liberation of free iodine.

Crystalline 1-iodo-1-desoxy-diacetonesorbose was found to be an unstable compound. It decomposed in a few weeks at room temperature to a black tarry mass but it could be stored for several weeks at 4°. Solutions in organic solvents at 25° darkened in a few days if exposed to light. Good qualitative tests for iodine were obtained using hot concentrated nitric acid to decompose the compound. However, hot 10% potassium hydroxide solutions only partially decomposed the iodo derivative in five minutes.

1-Iodo-1-desoxy-L-sorbose was prepared by hydrolysis of 1-iodo-1-desoxy-diacetonesorbose with glacial acetic acid and water by the method used by Raymond (10) on 6-iodo-6-desoxy-diacetonegalactose. This method was found to be more satisfactory than the hydrochloric acid hydrolysis method (12). 1-Iodo-1-desoxysorbose was found to be so unstable that aqueous solutions decomposed and liberated free iodine while being purified and even at 4° free iodine was liberated.

The starting material 1-tosyl-diacetone-L-sorbose was further characterized by conversion to its parent substance, 1-tosyl-L-sorbose, a known compound. It is probable that step-wise iodination of other C_1 tosyloxyl esters adjacent to a keto group may be accomplished under the conditions described.

The lability of this type of iodo sugar suggests its use with active alcoholic groups and a suitable catalyst. New types of glycosides and esters might be prepared. Also, if di-sugar ethers similar to the type previously postulated (11) could be prepared they would be of interest for structure characterization.

Acknowledgment. We are indebted to Dr. Al Steyermark of the Microchemical Division of these laboratories and his co-workers for the microchemical analyses.

EXPERIMENTAL

*1-Tosyl-2,3;4,6-diisopropylidene-*L*-sorbose.* Distilled 2,3; 4,6-diisopropylidene-L-sorbose was treated with *p*-toluenesufonyl chloride in dry pyridine. It was recrystallized from alcohol-water solutions, m.p. 101–102° $[\alpha]_D^{27}$ +2.8° (*c*, 5) in chloroform, for which m.p. 102–103°; and $[\alpha]_D^{28}$ +4.2° was previously reported (12).

Anal. Calc'd for $C_{19}H_{26}O_8S$: C, 55.03; H, 6.33; S, 7.74.

Found: C, 54.91; H, 6.06; S, 7.54.

*1-Tosyl-*L*-sorbose.* Eight grams of 1-tosyl-2,3;4,6-diisopropylidene-L-sorbose was dissolved in 100 ml. of glacial acetic acid immersed in a boiling water-bath. One hundred ml. of water was added gradually over 30 min. and heating was continued for 2.5 hours. Charcoal was added, the material filtered, concentrated *in vacuo* to 50 ml., and dehydrated twice by the addition of 50 ml. of ethanol and concentration. The syrup crystallized from a mixture of alcohol, ether, and petroleum ether; yield 4 g., m.p. 119–120°, $[\alpha]_D^{27}$ −13.8° in pyridine (*c*, 5) for which m.p. 116° and $[\alpha]_D^{20}$ −13.2° had been reported (12).

Anal. Calc'd for $C_{13}H_{18}O_8S$: C, 46.70; H, 5.43; S, 9.59.

Found: C, 46.76; H, 5.43; S, 9.66.

*1-Iodo-1-desoxy-2,3;4,6-diisopropylidene-*L*-sorbose.* Eight grams of 1-tosyl-2,3;4,6-diisopropylidene-L-sorbose, 100 ml. of acetone and 20 g. of sodium iodide were heated for 100 hours at 100° under 1000 lbs. nitrogen pressure. On cooling, the regenerated sodium *p*-toluenesulfonate was removed by filtration, the acetone removed *in vacuo* under 35°, and the residue extracted three times with ether.

The ether extracts were combined and washed with dilute sodium thiosulfate solution and water. On drying and concentration under 35°, the sirupy residue crystallized from alcohol diluted with water to the haze point. Analysis indicated approximately 50% conversion to the iodo derivative.

The procedure was repeated at 100° for 100 hours on the dried crystalline material, using a weight of sodium iodide equivalent to the compound. Five recrystallizations from aqueous alcohol served to purify the readily crystalline product for analysis. The pure compound proved to be unstable at room temperature; after a few days in the air it decomposed to a black tarry mass; m.p. 82–83° $[\alpha]_D^{28}$ −22.5° in chloroform (*c*, 4). For analysis the substance was dried for 4 hours at 25° over P_2O_5 *in vacuo* and was subsequently stored at 0°.

Anal. Calc'd for $C_{12}H_{19}IO_5$: C, 38.93; H, 5.17; I, 34.28.

Found: C, 39.64; H, 5.32; I, 34.68.

All attempts to improve the purity of the sample by other methods resulted in decomposition characterized by appearance of black specks in the sample, which spread to engulf the substance.

SUMMARY

The replacement of a C_1 tosyloxyl ester adjacent to a keto group by iodine has been accomplished by step-wise iodination using sodium iodide in acetone to produce 1-iodo-2,3; 4,6-diisopropylidene-L-sorbose as a crystalline compound.

NUTLEY, N. J.

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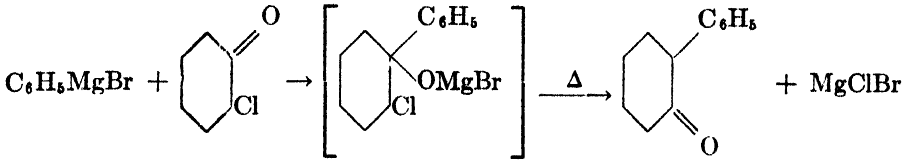
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

THE REACTION OF PHENYLMAGNESIUM BROMIDE WITH 2-CHLORO-4-METHYLCYCLOHEXANONE[1]

MELVIN S. NEWMAN AND WILLIAM T. BOOTH, JR.[2]

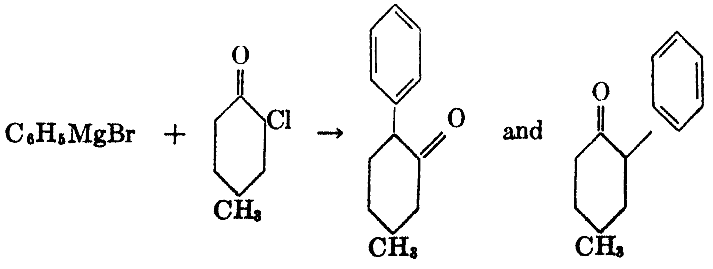
Received June 5, 1947

In previous research on the synthesis of hydroaromatic phenanthrene derivatives, 2-chlorocyclohexanone was reacted with phenylmagnesium bromide to yield 2-phenylcyclohexanone (1). It is well known that this result is not produced by a direct replacement of the chlorine atom by phenyl, but rather by an addition of the Grignard reagent to the carbonyl group followed by loss of magnesium halide, as follows:



It is not known whether the phenyl group in the ketonic product is attached to the carbon which originally formed the carbonyl group or to the carbon which was linked to the chlorine. In this case it is unimportant, as the structure of the final product is the same in either case. However, should there be another substituent in the ketonic ring, different products would result. The object of this investigation was to examine this phase of the reaction.

It has been shown that the reaction of alkylated 2-chlorocyclohexanones with alkyl Grignard reagents results in products in which the entering alkyl group is attached to the carbon which was attached to the chlorine (2). Since we were more interested in aryl Grignard reagents, we have studied the reaction of phenylmagnesium bromide with 2-chloro-4-methylcyclohexanone. The products, I and II, which might be formed are shown below.



I II

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[1] The material herein presented was contained in the Ph.D. thesis of W. T. B., Ohio State University, March 1947.

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The product obtained proved to be a mixture of ketones whose composition was exceedingly difficult to determine. After reduction, dehydration, dehydrogenation, and oxidation, a mixture of approximately three parts of *m*-phenylbenzoic acid and one part of *p*-phenylbenzoic acid was obtained. Because of losses along the way, this ratio is only an approximation of the quantities of I and II originally formed. However, the fact that a mixture of isomers was produced proves that the bromomagnesium derivative of the 1-phenyl-2-chloro-4-methylcyclohexanol initially formed in the Grignard reaction rearranges in part to produce a product in which the phenyl group is attached to the carbon which originally held the chlorine. For this reason, the synthetic value of this reaction is considerably decreased.

Our reaction series was carried out with 2-chloro-4-methylcyclohexanone which was probably almost entirely one of the inactive isomers. However, in view of the previous work on isomeric alkylchloro ketones (2), it is likely that a similar result would have been obtained if the other isomer had been used.

EXPERIMENTAL[3]

2-Chloro-4-methylcyclohexanone. 4-Methylcyclohexanone was chlorinated essentially as described for cyclohexanone (1) to yield 73% of chlorinated ketone together with 25% of recovered ketone. The product was separated into two fractions, b.p. 76–78° and 96–98° at 10 mm., by distillation. The lower-boiling isomer forms about two-thirds of the freshly prepared product but on heating and standing the proportion of the higher-boiling isomer rises to about 75%.[4]

Phenylmethylcyclohexanones. To a solution of 600 cc. of 2 *M* phenylmagnesium bromide was added with cooling 177 g. (1.2 moles) of lower-boiling chloro ketone. After stirring at room temperature for one hour, 600 cc. of xylene was added and the ether was removed by distillation. The xylene solution was refluxed for eight hours during which it changed from a clear orange solution to a semi-solid purple mass. After hydrolysis with ammonium chloride solution there was isolated 150 g. (67%) of phenylmethylcyclohexanones, b.p. 125–135°, at 3 mm. On redistillation, the majority boiled at 116–117° at 1 mm.

Anal.[a] Calc'd for $C_{13}H_{16}O$: C, 82.9; H, 8.6.
Found: C, 83.1; H, 8.9.

The 2,4-dinitrophenylhydrazone of the ketone mixture was prepared in 95% yield. After several recrystallizations, a fraction, m.p. 117–121°, was obtained as bright orange-red plates. The entire remaining derivative was collected, and melted over the range 89–112°.

Anal. Calc'd for $C_{19}H_{20}N_4O_4$: C, 61.9; H, 5.5; N, 15.2.
Found (for 117–121° crystals):[b] C, 62.3, 62.3; H, 5.6, 5.7; N, 15.1, 15.3.
(for 89–112° crystals):[a] C, 61.6; H, 5.5.

Phenylmethylcyclohexanols. The ketone mixture was reduced by the Meerwein-Ponndorf method to yield 98% of a mixture of alcohols, b.p. 129–130° at 4 mm. or 277° at 746 mm.

Anal.[a] Calc'd for $C_{13}H_{18}O$: C, 82.0; H, 9.5.
Found: C, 81.6; H, 9.5.

Methylbiphenyls. The above alcohol mixture was treated with thionyl chloride in pyridine-ether, and the whole refluxed for one hour. The phenylmethylcyclohexene mixture, b.p. 105–106° at 2 mm., was obtained in 88% yield. By heating 12.9 g. of this mixture with

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[3] All melting points corrected, boiling points uncorrected. Analyses marked [a] by the Arlington Laboratories, Fairfax, Virginia; marked [b] by W. J. Polglase, Ohio State University.

[4] Godchot and Bedos (2b) reported the boiling points of the isomers as 80–82° and 110–112° at 12 mm., but made no mention of their ratio.

4.8 g. of sulfur from 200° to 240° during three hours there was obtained 7.5 g. (60%) of a mixture of methylbiphenyls, b.p. 132–133° at 9 mm., 264–265° at 739 mm. For comparison ortho-, meta-, and para-methylbiphenyl were synthesized in 8, 6, and 6% yields respectively by the Gomberg method (3, 4). The boiling point of the unknown mixture of biphenyls corresponded to that of the meta or para isomer but differed from the ortho (b.p. 125° at 9 mm., 251° at 739 mm.). Attempts to prepare the solid 4-nitro-4′-methylbiphenyl (3) or 4,4′-dinitro-3′-methylbiphenyl (5) from the methybiphenyl mixture were unsuccessful.

Preparation and separation of phenylbenzoic acids (*6*). To a solution of 14.2 g. of potassium permanganate in 350 cc. of water was added 5 g. of the methylbiphenyl mixture, and the whole was refluxed until the permanganate was decolorized. The acid fraction thus produced was separated, and the neutral portion refluxed again with a solution of 5.6 g. of potassium permanganate in 125 cc. of water. There was thus obtained 3.6 g. (61%) of acid, m.p. 128–158°. An ether solution of one gram of the acids was shaken with 10% sodium carbonate solution. The insoluble sodium salt was collected, washed with ether, and acidified to yield 0.18 g. of *p*-phenylbenzoic acid, m.p. 222–224°. From the water-soluble sodium salts was obtained 0.70 g. of acid mixture, m.p. 143–158°. Recrystallization yielded mostly *m*-phenylbenzoic acid, m.p. 158–160°.

SUMMARY

It has been shown that when phenylmagnesium bromide reacts with 2-chloro-4-methylcyclohexanone, the final product is a mixture of 2-phenyl-4-methylcyclohexanone and 2-phenyl-5-methylcyclohexanone.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

THE SYNTHESIS OF LAURIC ACID AND DODECYLAMINE CONTAINING CARBON FOURTEEN[1]

H. J. HARWOOD AND A. W. RALSTON

Received June 23, 1947

Compounds labeled by radioisotopes have been shown to be of great value in investigations of chemical and physical mechanisms (1). The application of such compounds to studies involving the behavior of long-chain aliphatic compounds is clearly indicated. Obviously the first step is the synthesis of the labeled substances. This paper describes the preparation of lauric acid and dodecylamine containing C^{14} in the 1-position.

In the proposed application, an activity of approximately 0.02 millicurie per gram of reagent was considered desirable. C^{14} was obtained in the form of barium carbonate having a radioactive isotope ratio of 3.16% and an activity of 1 millicurie in 124.3 mg. The radioactive carbon was introduced into the aliphatic carbon chain by the reaction of carbon dioxide with undecylmagnesium bromide. The radioactive lauric acid so obtained was converted to the nitrile by passage over aluminum oxide in the presence of ammonia (2). Reduction of the nitrile with sodium yielded radioactive dodecylamine which was isolated as the acetate. Successive additions of inert materials at each step of the synthesis served to reduce losses of the active compounds as well as to achieve the desired activity in the final products. Radioactive assay indicated that no appreciable loss of C^{14} had occurred.

EXPERIMENTAL PART

Radioactive lauric acid. Undecylmagnesium bromide was prepared from 14.1 g. of undecyl bromide (from undecanol-1, f.p. 16.2°) and 1.5 g. of magnesium in 125 cc. of anhydrous ethyl ether. The solution containing the Grignard reagent was cooled to about −40° and into it was passed the carbon dioxide liberated from 0.5 g. of barium carbonate by means of concentrated sulfuric acid. This barium carbonate contained 0.0392 g. of the original radioactive salt with an activity of 0.315 millicurie. A stream of nitrogen (25 cc. min.) carried the active carbon dioxide into the Grignard reagent, which was vigorously stirred. After about forty minutes the stream of nitrogen was increased to 100 cc./min. for ten minutes. Carbonation of the Grignard reagent was completed using inert carbon dioxide gas (50–100 cc./min.), and the temperature was allowed to rise to 25° during the process.

After hydrolysis with dilute hydrochloric acid, the ether solution was washed with water until the washings were neutral. Evaporation of the ether yielded a mixture of lauric acid and hydrocarbon (undecane and docosane) which were separated by extraction of the dilute alcohol solution of potassium laurate with petroleum ether (b.p. 60–70°). Partial evaporation of the potassium laurate solution to remove petroleum ether and alcohol, followed by acidification, yielded lauric acid, which was filtered off, washed with water, and crystallized from acetonitrile at −20°. The crystallized acid weighed 6.80 g. (f.p. 43.52°). Evaporation of the filtrate yielded 0.7 g. of residual acid. To this residue was added 3.0 g. of inert lauric acid (f.p. 43.95°) and the mixture crystallized from 30 cc. of acetonitrile at −20°. A second crop weighing 3.30 g. was obtained. Evaporation of this filtrate yielded 0.4 g. of residue which was discarded. The combined lauric acid fractions (10.10 g.) had the freezing point 43.40.°

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[1] These compounds were synthesized for use in connection with a fellowship sponsored by Armour and Company under the direction of Professor A. M. Gaudin of Massachusetts Institute of Technology. The project involves the application of radioactive tracer technique to a study of the mechanism of mineral flotation.

A portion (6.73 g.) of the lauric acid was used in the preparation of lauronitrile, and the remainder (3.37 g.) was further diluted with 1.63 g. of inert lauric acid and crystallized from 25 cc. of acetonitrile at −20°. This acid (4.7 g.) had the capillary melting point 44.2–44.7° (cor.) and an activity of 0.10 millicurie.

Radioactive lauronitrile. The 6.73-g. portion of radioactive lauric acid was converted to nitrile by passage over aluminum oxide catalyst in a stream of ammonia gas. The ammonia rate was 200 cc./min. and the acid was vaporized by being dropped into a flask at 320–340°. Approximately 10 g. of catalyst was used at a temperature of 390°. The catalyst chamber was 22 x 1.6 cm. and contained a 7.25-mm. (O.D.) thermocouple well. A 3.23-g. portion of inert lauric acid was passed through the apparatus after the active sample. A total time of 130 min. was required, and the apparatus was swept with ammonia for an additional 60 min. after all the acid had been added. The product was collected in petroleum ether, washed with water, and dried over potassium carbonate. After removal of the solvent, a yield of 8.82 g. (97.4%) of crude radioactive lauronitrile was obtained. This nitrile was converted to amine without purification.

Radioactive dodecylamine. To 6 g. of finely divided sodium, vigorously stirred in 75 cc. of boiling toluene, was added the 8.82 g. of radioactive lauronitrile in 19 g. of anhydrous butanol-1. The addition required 10 minutes. An additional 25 cc. of toluene and 10 cc. of butanol were added and the mixture heated and stirred until the sodium had all reacted. Water was cautiously added, the lower layer separated, and the toluene solution dried with potassium carbonate.

After removal of the solvent, the crude amine was dissolved in 100 cc. of 50% ethanol containing 4 cc. of concentrated hydrochloric acid. This solution was extracted four times with petroleum ether (b.p. 60–70°) to remove unreduced nitrile. The solution of amine hydrochloride was boiled to remove most of the ethanol, and then made alkaline. The amine was extracted with petroleum ether and the solution dried with potassium carbonate. Evaporation of the solvent yielded 8.25 g. (91.5%) of radioactive dodecylamine. This amine was dissolved in 50 cc. of benzene, 2.5 cc. of glacial acetic acid added, and the acetate crystallized at 15°. After recrystallization from 50 cc. of benzene at 15°, a yield of 9.5 g. of radioactive dodecylammonium acetate was obtained. This salt had the capillary melting point 68.5–69.0° (cor.) and an activity of 0.24 millicurie.

ACKNOWLEDGMENT

The authors wish to make acknowledgment to Dr. Warren W Miller of Massachusetts Institute of Technology for the radioactive assay. The method used has been previously described by Dr. Miller (3).

SUMMARY

The preparation of lauric acid and dodecylamine containing C^{14} has been reported.

Chicago 9, Ill.

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[CONTRIBUTION FROM THE BATTELLE MEMORIAL INSTITUTE]

6,8-DIIODOBENZOYLENEUREA, AND THE INTERACTION OF 5,7-DIHALOGENOISATOIC ANHYDRIDES WITH AMMONIA AND WITH ETHYLAMINE. 3-ETHYL-6,8-DIHALOGENOBENZOYLENEUREAS

FRED E. SHEIBLEY

Received August 6, 1946

The reaction of isatoic anhydride and its derivatives with ammonia or primary amines to produce 2-aminobenzamides is sufficiently general (1) for the formation of benzoyleneureas in two instances to have been overlooked. In a study (2) of the behavior of 5,7-dichloroisatoic anhydride with ammonia, it was shown that one of the products of the reaction, previously reported to be 3,5-dichloro-2-aminobenzamide, is actually 6,8-dichlorobenzoyleneurea, and a like mistake was suspected in the case of the dibromo derivatives. This suspicion has been confirmed and the investigation has been extended to include 6,8-diiodobenzoyleneurea and related compounds. The syntheses and reactions of these three series of compounds, respectively dichloro, dibromo, and diiodo derivatives, are similar and are outlined concordantly below.

6,8-Diiodobenzoyleneurea as a Reagent for Sodium

The use of 6,8-dibromo- and especially 6,8-dichloro-benzoyleneurea as reagents for the detection of sodium in the presence of other alkali metals was suggested in previous papers (2, 3). The analogous 6,8-diiodobenzoyleneurea is not a reagent for sodium because of the sparing solubility and ready hydrolysis of its alkali metal salts. Preparations of the sodium salt, obtained by precipitating solutions of the urea in aqueous lithium hydroxide with sodium chloride, have a variable composition and are evidently mixtures of 6,8-diiodobenzoyleneurea and its hydrated monosodium salt. Possibly some of the isomeric dichlorobenzoyleneureas will prove useful as reagents for sodium, and this approach is being investigated.

Fusion of 3,5-Dihalogenoanthranilic Acids with Urea

When 3,5-dihalogenoanthranilic acids (I) are fused with urea, 6,8-dihalogenobenzoyleneureas (V) and 3,5-dihalogeno-2-aminobenzamides (IV) are formed. The detection of both of these products in a single experiment was initially effected (4) with 3,5-dichloroanthranilic acid but subsequent trials with 3,5-diiodoanthranilic acid and a repetition of the fusion of urea with 3,5-dibromoanthranilic acid (3) demonstrate the generality of this reaction for all three of the acids (I). The yields of products (IV, V) from fusions of the three acids (I) with urea, conducted at the same temperature, vary regularly with the increase in weight of the halogen substituents and are compared in Table I.

Nuclear-substituted anthranilic acids, considered as monobasic acids, are an exception to the observation (5) that aromatic monobasic acids do not give amides on fusion with urea, for recent work (6) has shown that 3-nitro- and 4-nitro-anthranilic acids also furnish the corresponding amides and benzoyleneureas by this treatment although 5-nitro- and 3,5-dinitro-anthranilic acids (7, 8) fail to react. Anthranilic acid itself, fused with 1.5 moles of urea at 120° during two hours, gave 16% of benzoyleneurea, but any *o*-aminobenzamide which may have been formed in the reaction was not detected.

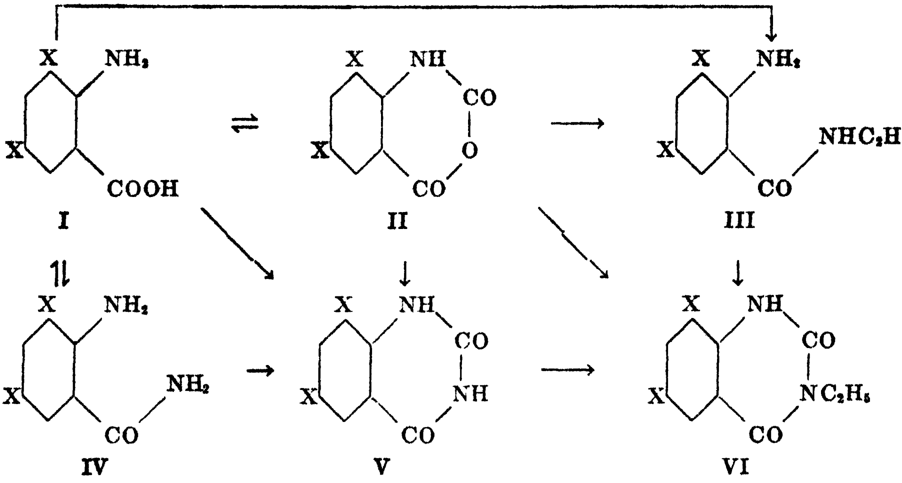

TABLE I

YIELDS OF CRUDE PRODUCTS FROM FUSIONS OF 3,5-DIHALOGENOANTHRANILIC ACIDS AND UREA AT 160°

ANTHRANILIC ACID (I)	MOLAR RATIO, UREA:ACID	TIME, HOURS	BENZOYLENE-UREA (V), %	2-AMINOBENZ-AMIDE, (IV), %
Dichloro[a]	3.43	4	67	11
Dibromo[b]	3.34	7	45	40
Diiodo[b]	3.24	7	23	69

[a] Data from (4).

[b] This paper.

3,5-Diiodo-2-aminobenzamide has been prepared (9) from diiodoanthranilic acid with phosphorus pentachloride and ammonium carbonate; this method is applicable to the dichloro and dibromo acids (I), but attempts to apply it to anthranilic acid were unsuccessful.[1] The constitution (IV) of the three dihalogenoaminobenzamides is indicated by their alkaline hydrolysis to the parent acids (I) and by their conversion to the benzoyleneureas (V) with ethyl chlorocarbonate (11). Prepared in this way, from the amides and ethyl chlorocarbonate, the benzoyleneureas (V) are pure white in color, a quality which is difficult to attain in these compounds by the other methods of preparation.

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[1] The compound, $ClCOC_6H_4NHPOCl_2$, from anthranilic acid and phosphorus pentachloride, is said (10) to give *o*-aminobenzamide with aqueous ammnonia.

Interaction of 5,7-Dihalogenoisatoic Anhydrides and Ammonia

3,5-Dichloro- and 3,5-dibromo-2-aminobenzamide were first recorded in 1885 by Robert Dorsch[2] who assigned the constitution IV to two products which he obtained by treating 5,7-dichloro- and 5,7-dibromo-isatoic anhydride, respectively, with aqueous ammonia. Repetitions (13) of his experiments, however, invariably yielded the corresponding benzoyleneureas (V) and anthranilic acids (I) in proportions required by the equation,

$$\underset{\substack{\text{Dihalogeno-}\\ \text{isatoic}\\ \text{Anhydride (II)}}}{5C_8H_3O_3NX_2} + 2NH_3 + H_2O \rightarrow \underset{\substack{\text{Dihalogeno-}\\ \text{benzoylene}\\ \text{urea (V)}}}{2C_8H_4O_2N_2X_2} + \underset{\substack{\text{Dihalogeno-}\\ \text{anthranilic}\\ \text{Acid (I)}}}{3C_7H_5O_2NX_2} + 3CO_2,$$

which applies equally well to the behavior of 5,7-diiodoisatoic anhydride with ammonia. For his dichloro amide Dorsch (14) gave the melting point 284° (an uncorrected melting point of 6,8-dichlorobenzoyleneurea) and a nitrogen determination which is 1.3% high for dichlorobenzoyleneurea; for his dibromo amide he gave the melting point 196–197° and determinations of four elements which are in good agreement with the calculated composition of the amide. But 3,5-dibromo-2-aminobenzamide, prepared from 3,5-dibromoanthranilic acid by fusion with urea or by treatment with phosphorus pentachloride and ammonium carbonate, melts at 215.5° (corrected), the constitution IV being established for this product by its ready conversion to 6,8-dibromobenzoyleneurea with ethyl chlorocarbonate, and by an easy hydrolysis to the anthranilic acid. Dorsch's products, therefore, must have been 6,8-dichloro- and 6,8-dibromo-benzoyleneurea, and the melting point 196–197° is a misprint for 296–297°, an uncorrected melting point of 6,8-dibromobenzoyleneurea. Subsequent investigators (15) were unable to repeat certain parts of Dorsch's work and concluded that the tri- and tetra-bromoanthranilic acids which he described (16) were specimens of tribromoaniline (17).

Interaction of 5,7-Dihalogenoisatoic Anhydrides and Ethylamine

On warming 5,7-dihalogenoisatoic anhydrides (II) with aqueous ethylamine, 3-ethyl-6,8-dihalogenobenzoyleneureas (VI) and 3,5-dihalogeno-2-aminobenzethylamides (III) are formed in variable amounts, depending upon the choice of the halogen substituents. The ethylamides (III) were identified by their synthesis from the anthranilic acids (I) with phosphorus pentachloride and ethylamine, and by conversion to the 3-ethylbenzoyleneureas (VI) on treatment with ethyl chlorocarbonate. The 3-ethylbenzoyleneureas (VI) are identical with the products of direct ethylation of the 6,8-dihalogenobenzoyleneureas (V), obtained by heating the latter with ethyl iodide and alkalies, and confirm the constitution previously assigned (18) to the ethylation product of 6,8-dibromobenzoyleneurea.

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[2] Robert Dorsch, Inaugural-Dissertation, Leipzig, 1885. The text is identical with the published article (12).

Preparation of 5,7-Dihalogenoisatoic Anhydrides

5,7-Dichloro- and 5,7-diiodo-isatoic anhydride (II) were prepared by refluxing the anthranilic acids (I) with ethyl chlorocarbonate. 5,7-Dibromoisatoic anhydride was obtained (13) by oxidizing tetrabromoindigo, but a better method of preparation, now being investigated, is the treatment of dibromoanthranilic acid with phosgene in glacial acetic acid solution. These anhydrides (II) dissolve in warm, aqueous sodium hydroxide, giving solutions which yield precipitates of the anthranilic acids (I) on acidification.

EXPERIMENTAL

3,5-Diiodoanthranilic acid (I). An Eastman preparation was crystallized from alcohol and recrystallized from benzene; needles, m.p. 234.5–235° (corr.).

6,8-Diiodobenzoyleneurea (V) from 3,5-diiodoanthranilic acid (I). Two grams of diiodoanthranilic acid and 1 g. of urea were mixed in a flask equipped with a loose-fitting cork stopper, carrying a vertical exit tube, and heated in an oil-bath at 160° during seven hours. The mixture just melted initially and then resolidified. The acicular sublimate (0.22 g.) which deposited on the flask walls was insoluble in aqueous sodium hydroxide, but the presence of diiodoaminobenzamide in it was not conclusively demonstrated.

The porous, yellow, reaction mixture (2.64 g.) was pulverized and treated with hot, dilute, aqueous sodium hydroxide; the undissolved material remaining from this treatment was warmed with dilute hydrochloric acid, washed with water, and extracted repeatedly with fresh portions of hot aqueous lithium hydroxide until a sample of the extract failed to give a precipitate with hydrochloric acid. The combined extracts crystallized on cooling; they were reheated to boiling and the clear solution was acidified with dilute acetic acid. The precipitate (0.51 g.) of diiodobenzoyleneurea which separated was washed with water, dried, and dissolved in 575 cc. of a boiling 1:1 mixture of acetone and alcohol. The solution was filtered, evaporated slowly on a steam-bath until crystals just began to form, and then allowed to cool; 6,8-diiodobenzoyleneurea (0.44 g.) crystallized in small, pale yellow needles, m.p. 326–327° (corr.) after sintering to larger crystals around 300°. The compound is soluble in hot glycol and crystallizes in flocs on cooling.

Anal. Calc'd for $C_8H_4I_2N_2O_2$: N, 6.77. Found: N, 6.74, 6.99, 6.69.

3,5-Diiodo-2-aminobenzamide (IV). The insoluble residue remaining from the extractions with aqueous lithium hydroxide described above was washed with dilute hydrochloric acid and with water, and dried. The crude, yellow amide (1.39 g.) thus obtained was dissolved in 250 cc. of boiling alcohol and the solution was filtered from a slight amount of deep yellow, insoluble material (possibly a tetraiodoacridone). On cooling, 3,5-diiodo-2-aminobenzamide (1.04 g.) crystallized in yellowish to pale brown, brittle needles, m.p. 241–242° (corr.); at 270° the black melt evolved iodine vapor.

Anal. Calc'd for $C_7H_6I_2N_2O$: N, 7.22. Found: N, 7.11.

Alkali metal salts of 6,8-diiodobenzoyleneurea are too insoluble to warrant their use as tests for sodium. The urea dissolves in hot aqueous lithium hydroxide to give solutions which rapidly deposit fine needles on cooling. It is slightly soluble in hot aqueous potassium hydroxide, and from the resulting solutions white needles separate in small amounts on cooling and standing. It is least soluble in hot aqueous sodium hydroxide; the solutions hardly crystallize on standing, and yield only slight, flocculent precipitates on acidification.

A solution of 6,8-diiodobenzoyleneurea in lithium hydroxide, sufficiently diluted to avoid rapid crystallization, gave a precipitate with a sodium chloride solution faster and more completely than it did with a solution of potassium bromide, and instantly yielded a gelatinous precipitate of the urea on adding ammonium chloride. A warm, somewhat stronger solution of the urea in lithium hydroxide gave crystalline precipitates with solutions of potassium, rubidium, and cesium chlorides, and also with pure water.

Sodium 6,8-diiodobenzoyleneurea, precipitated from hot solutions of the lithium salt, has a variable composition and appears to be a mixture of the free urea and its hydrated monosodium salt. Equal weights, 0.2 g., of diiodobenzoyleneurea and lithium hydroxide were dissolved in 75 cc. of boiling water, the solution was filtered, and 25 cc. of 0.5 *M* sodium chloride was added. Precipitation began immediately. After the suspension had stood for 1–3 hours, the light, crystalline precipitate was collected, washed with water, and dried at 40° during 2–3 days; yield, 0.21–0.25 g.

In a series of drying experiments conducted with four different samples prepared as described above, the losses, on attaining constant weights, varied from 1.29% after one day at 120° to 4.58% after fifteen days over concentrated sulfuric acid. The hygroscopic products were finally ignited with sulfuric acid and the residues (negative lithium flame tests) weighed as sodium sulfate. The sodium contents, based on the initial samples, varied from 2.68 to 4.17%.

5,7-Diiodoisatoic anhydride (*II*). A mixture of 0.44 g. of diiodoanthranilic acid and 2 cc. of ethyl chlorocarbonate was gently refluxed over a small flame during 21 hours. A mixture of solid and liquid resulted. Most of the liquid was allowed to evaporate spontaneously, and the solid was crushed, washed with alcohol, and dried; 0.38 g. Crystallization from benzene yielded 0.24 g. of short, glistening, yellow needles, m.p. 264–265° (corr.). Preparations on a larger scale resulted in lower yields. Repeated attempts to prepare the corresponding dibromoisoatoic anhydride by this method were unsuccessful and resort was had to the oxidation of tetrabromoindigo (13) in order to obtain a supply of this compound. 5,7-Diiodoisatoic anhydride is readily soluble in warm, dilute, aqueous sodium hydroxide, forming solutions which deposit diiodoanthranilic acid on acidification. The acicular habit of diiodoisatoic anhydride was unexpected and contrasts strikingly with the short, clear prisms of the dichloro and dibromo anhydrides.

Anal Calc'd for $C_8H_3I_2NO_3$: N, 3.38. Found: N, 3.06, 3.29.

6,8-Diiodobenzoyleneurea (*V*) *from 5,7-diiodoisatoic anhydride* (*II*). Suspensions of the anhydride (0.393, 0.5405 g ; 5, 5 moles basis) in 20-cc. portions of aqueous 28% ammonia were refluxed gently on a water-bath during one hour. On cooling, the undissolved residues of diiodobenzoyleneurea (0.122, 0.2225 g.; 1.56, 2.06 moles) were collected, washed with water, and dried. The respective filtrates and washings were acidified hot with dilute acetic acid and the diiodoanthranilic acid was allowed to crystallize (0.227, 0.2915 g.; 3.08, 2.88 moles). These products were identified by crystallizations from the usual solvents and mixture melting points with known specimens.

3,5-Dibromoanthranilic acid (*I*) was prepared exactly as described by Wheeler and Oates (19), and was shown to be identical (mixture melting point) with the acid, m.p. 235–236° (corr.) previously obtained (13) by the action of ammonia on 5,7-dibromoisatoic anhydride.

3,5-Dibromo-2-aminobenzamide (*IV*). (a) A mixture of 2 g. of dibromoanthranilic acid and 1.36 g. of urea was maintained at 160° during seven hours as described above for the preparation of diiodobenzoyleneurea. The mixture melted and bubbled just below this temperature and then slowly solidified to a yellow mass. The white, acicular sublimate (0.41 g.), washed with water, dried, and crystallized from alcohol, was found to consist principally of dibromoaminobenzamide. The yellow residue (2.52 g.) was powdered and extracted three times with hot, aqueous lithium hydroxide, an acidified test portion from the final extraction remaining clear. The combined extracts were acidified and the resulting precipitate was collected, washed with water, and extracted with warm, aqueous sodium hydroxide. The insoluble sodium salt, washed with water and treated with warm, dilute hydrochloric acid, yielded 0.97 g. of crude 6,8-dibromobenzoyleneurea, m.p. 291–292° after washing and drying. Acidification of the sodium hydroxide extract precipitated 0.10 g. of material not identical with dibromoanthranilic acid.

The residue (0.79 g.) insoluble in lithium hydroxide was taken up in boiling alcohol, only a small amount of yellow material remaining undissolved. From the alcoholic solution, on cooling, 3,5-dibromo-2-aminobenzamide separated in long, flat, glistening prisms; m.p. 215.5–216° (corr.).

Anal. Calc'd for $C_7H_6Br_2N_2O$: N, 9.53. Found: N, 9.20, 9.73.

(b) Two-tenths gram of phosphorus pentachloride was added to a suspension of 0.25 g. of dibromoanthranilic acid in 10 cc. of benzene and the mixture was allowed to stand in a stoppered flask at room temperature during five hours, with occasional shaking. The solution was filtered from undissolved solids and allowed to stand overnight with an excess of powdered ammonium carbonate. The white solids were collected, washed with benzene, dried, and the ammonium salts leached out with water. The water-insoluble residue, crystallized from alcohol, did not depress the melting point of a sample of the 3,5-dibromo-2-aminobenzamide described under (a).

3,5-Dichloro-2-aminobenzamide (IV), identical with an authentic specimen (2), was similarly prepared from dichloroanthranilic acid and phosphorus pentachloride except that the bulk of the product, in this case, was found in the benzene solution rather than in the ammonium salt residues.

Alkaline hydrolysis of the amides (IV). 3,5-Dibromo-2-aminobenzamide was completely dissolved after two hours of refluxing with aqueous sodium hydroxide, whereas the diiodo compound required twelve hours of the same treatment to effect complete solution. The dichloro amide is approximately intermediate (2) between these extremes. Acidification of the alkaline solutions produced precipitates of the corresponding anthranilic acids. The dibromo acid thus obtained was crystallized once from benzene; m.p. 235.5–236° (corr.) in exact agreement with the observation of Bogert and Hand (20).

Interaction of the amides (IV) with ethyl chlorocarbonate. 6,8-Diiodobenzoyleneurea (V) from 3,5-diiodo-2-aminobenzamide (IV). Twelve cc. of ethyl chlorocarbonate was added to 0.95 g. of the diiodo amide, and the mixture was gently refluxed during three hours. Reaction took place readily but frequent shaking was necessary in order to prevent the voluminous, fine white particles of product from coating the larger crystals of amide. The suspension was boiled with 20 cc. of alcohol, allowed to cool, and the white, insoluble diiodobenzoyleneurea (0.72 g.) was washed with alcohol.

The dibromo- and dichloro-aminobenzamides reacted similarly, the corresponding benzoyleneureas being obtained and identified, after crystallizations from acetone-alcohol or alcohol, by mixture melting points with known specimens. All three of these products were pure white in color.

Interaction of the dihalogenoisatoic anhydrides (II) with ethylamine: 3-Ethyl-6,8-dihalogenobenzoyleneureas (VI), and 3,5-dihalogeno-2-aminobenzethylamides (III). One-half gram of the anhydride was treated with 15 cc. of aqueous, 22% ethylamine (an immediate reaction was evident), and the resulting suspension was heated, with frequent shaking, under a reflux condenser on a water-bath during one hour. A part or all of the solids dissolved, but after 20 minutes, crystals began to separate from the hot solution. Sixty cc. of aqueous 0.4 *M* sodium hydroxide was added; the mixture was boiled, allowed to cool, and the undissolved residue of dihalogenoaminobenzethylamide removed. When diiodoisatoic anhydride was used the filtration was performed with the hot solution since the sodium salt of ethyldiiodobenzoyleneurea crystallizes readily on cooling, and the by-product, ethylamide, is not appreciably soluble; the dichloro and dibromo ethylamides are slightly soluble under these conditions. Addition of acetic acid to the alkaline filtrate precipitated the ethyldihalogenobenzoyleneurea. The yields of crude products, properties, and analytical data observed with these ethyl derivatives are given in Table II.

3,5-Diiodo-2-aminobenzethylamide (III). Two grams of diiodoanthranilic acid and 1.2 g. of phosphorus pentachloride were suspended in 15 cc. of benzene. After standing for one hour at room temperature, shaking frequently, the solution was filtered from undissolved solids and treated slowly, while shaking, with 25 cc. of aqueous, 12% ethylamine. A white precipitate rapidly formed and, after aging overnight, was collected, pressed, washed with water, and dried at 100°; yield 1.45 g. Evaporation of the water-washed, yellow benzene layer gave an additional 0.39 g. of impure product. From these crude products hot, dilute, aqueous sodium hydroxide removed small amounts of alkali-soluble material, precipitable by acids. The residues insoluble in alkali were crystallized from a mixture of benzene and petroleum ether and then repeatedly crystallized from dilute alcohol. 3,5-Diiodo-2-amino-

TABLE II

Reaction Products of 5,7-Dihalogenoisatoic Anhydrides with Ethylamine

COMPOUNDS	% YIELD, CRUDE	APPEARANCE	M.P., °C., CORR.	FORMULA	ANALYSES[a]			
					Calc'd		Found	
					C	H	C	H
3-Ethylbenzoyleneureas								
6,8-Dichloro-	71	Long, slender needles from alcohol	244.5–245	$C_{10}H_8Cl_2N_2O_2$	46.35 N, 10.83	3.11	46.66 N, 10.72	3.79
6,8-Dibromo-	86	Like dichloro	252.5–253	$C_{10}H_8Br_2N_2O_2$	34.51	2.32	34.91	2.46
6,8-Diiodo-	87	Scales from glycol	275–276	$C_{10}H_8I_2N_2O_2$	27 17	1.82	27.50	2.07
2-Aminobenzethylamides								
3,5-Dichloro-	15	Silky, hair-like needles from petroleum ether	161.5	$C_9H_{10}Cl_2N_2O$	46.37	4.32	46.45 46.37	—[b]
3,5-Dibromo-	8.2	Sheaves of short needles from benzene + petroleum ether	174–174.5	$C_9H_{10}Br_2N_2O$	33.57	3.13	33.41	3.45
3,5-Diiodo-	5 5	Papery mass of small needles from dilute alcohol	213	$C_9H_{10}I_2N_2O$	25.98	2.42	25.93 25.54	2.65[c] 2.83

[a] Determinations by J. S. McNulty

[b] This compound was triboelectric and difficult to burn, and good hydrogen values were not obtained.

[c] Sample prepared directly from diiodoanthranilic acid.

benzethylamide was not appreciably attacked by long heating with strong, aqueous sodium hydroxide; the material which did dissolve was precipitated by acid but was not identical with 3,5-diiodoanthranilic acid.

The corresponding dibromo- and dichloro-aminobenzethylamides were similarly prepared, except that these compounds remained dissolved in the benzene layers. All three of these substances proved to be identical (mixture melting points) with the alkali-insoluble products obtained, as described above, by the action of ethylamine on the corresponding dihalogenoisatoic anhydrides.

Interaction of the 3,5-dihalogeno-2-aminobenzethylamides (III) with ethyl chlorocarbonate: 3-Ethyl-6,8-dihalogenobenzoyleneureas (VI). All three of the N-ethylamides dissolved readily in warm ethyl chlorocarbonate. The solutions were evaporated to dryness on a steam-bath and the white, crystalline residues taken up in hot, aqueous sodium hydroxide. The alkaline solutions were filtered from small amounts of insoluble, red-brown, crystalline materials, and acidified, the 3-ethylbenzoyleneureas which precipitated were washed with water, dried (yields 65–72%), and crystallized from suitable solvents before comparison with the identical products by the other two methods of preparation.

Direct ethylation of 6,8-dihalogenobenzoyleneureas (V): 3-Ethyl-6,8-dihalogenobenzoyleneureas (VI). Ethylations were effected by heating the benzoyleneureas with solutions of ethyl iodide and caustic alkalies in dilute alcohol, following the procedure described previously (18) for the preparation of 3-ethyl-6,8-dibromobenzoyleneurea. Potassium hydroxide was used with the dichloro, and lithium hydroxide with the dibromo and diiodo compounds. The yields of precipitated dichloro, dibromo, and diiodo products were 80, 83 (18), and 55%, respectively. These ethylated compounds are identical with and did not depress the melting points of the corresponding alkali-soluble products obtained from the isatoic anhydrides with ethylamine, and from the aminobenzethylamides with ethyl chlorocarbonate.

Color reactions of the benzoyleneureas. Mixtures of approximately equal bulks of the benzoyleneureas and resorcinol were moistened with concentrated sulfuric acid and heated until fumes issued from the mouths of the containers. The cold melts were taken up in water (only the melt with benzoyleneurea dissolved completely) and made alkaline with sodium hydroxide. Benzoyleneurea and dichlorobenzoyleneurea gave yellow colors. Dibromobenzoyleneurea gave a yellow color which turned pink within a few minutes. Diiodobenzoyleneurea gave a pale pink color. These colors fluoresced slightly; they faded with hydrochloric acid and were not completely restored by alkali.

The marked fluorescent property usually exhibited by solutions of the dichloro compounds, the amide, the acid, and the benzoyleneurea (2), is lacking in solutions of the dibromo and diiodo derivatives.

SUMMARY

6,8-Diiodobenzoyleneurea is not a reagent for sodium because of the low solubility and ready hydrolysis of its alkali metal salts. 6,8-Dichlorobenzoyleneurea remains more suited to this purpose.

The fusion of 3,5-dihalogenoanthranilic acids (dichloro, dibromo, and diiodo) with urea yields 6,8-dihalogenobenzoyleneureas and 3,5-dihalogeno-2-aminobenzamides. The latter also result on reacting the anthranilic acids with phosphorus pentachloride and ammonium carbonate, and are converted to the benzoyleneureas by treatment with ethyl chlorocarbonate.

5,7-Dihalogenoisatoic anhydrides, formed (excepting the dibromo derivative) by prolonged heating of the anthranilic acids with ethyl chlorocarbonate, react with ammonia to give the corresponding benzoyleneureas and anthranilic acids in yields of 40 and 60%, respectively. The dibromo and dichloro aminobenz-

amides reported by Dorsch in 1885 to result from this reaction were undoubtedly specimens of the benzoyleneureas.

When ethylamine instead of ammonia acts on 5,7-dihalogenoisatoic anhydrides the reaction follows an altered course, yielding 3-ethyl-6,8-dihalogenobenzoyleneureas and 3,5-dihalogeno-2-aminobenzethylamides in variable amounts. The 2-aminobenzethylamides result directly from the anthranilic acids by successive treatments with phosphorus pentachloride and ethylamine, and react with ethyl chlorocarbonate to give the 3-ethylbenzoyleneureas. The latter are obtained directly on ethylation of the parent 6,8-dihalogenobenzoyleneureas.

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[Contribution from the Polytechnic Institute of Brooklyn]

ELECTRONIC INTERPRETATION OF ORGANIC CHEMISTRY. I. THE ROLE OF SOLVENT IN DETERMINING REACTION RATE

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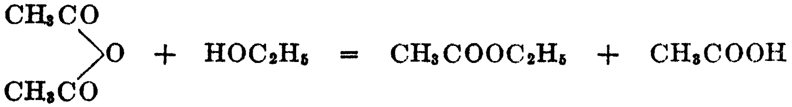
Solvents are known to affect profoundly the speed of an organic reaction. The main results have been summarized and discussed by Richardson and Soper (15), and the position has been recently reviewed with reference to current theories by Bell (1). The present paper is an attempt to coordinate and synthesize the existing ideas and results from the solvation standpoint alone, in the light of the recent developments in electronic interpretation as applied to organic chemistry, and to suggest a uniformity of treatment based on the current theories of hydrogen bonding and donor-acceptor mechanism.

The viewpoint to be presented herein utilizes only the basic concepts of organic chemists (14, 16) about electronegativity, inductive effect, and mesomeric or resonance effect, and also the idea of hydrogen bonding. The application of our concept can be best made clear with reference to specific cases as follows.

Esterification reactions. Let us consider the reaction, esterification of acetic anhydride according to the equation,



$$(CH_3CO)_2O + HOC_2H_5 = CH_3COOC_2H_5 + CH_3COOH$$

The master step evidently is a reaction between a donor and an acceptor center. We believe that the oxygen of the anhydride is attacked by the hydroxylic hydrogens of the alcohol, since the reaction speed is fastest with primary alcohols. However, to apply our concept, the exact isolation of the active centers is not necessary. Let us now consider how the solvent affects the above reaction. We believe that all solutes are solvated to a greater or lesser degree by the solvent, either by hydrogen bonds or by van der Waals forces. In the above case there will be hydrogen bond formation between the donor centers (oxygen) and the hydrogen of the solvent, the strength of this hydrogen bond depending on the electropositivity of the hydrogen present in the solvent. That hydrogen atoms attached to carbon differ widely among themselves in polarity, depending on the molecule in which they are present, is an admitted fact, and even quantitative data exist for the acidity of quite a few C—H bonds. That hydrogen atoms present in C—H bonds can engage themselves in hydrogen bonding in haloform type compounds has been shown by Copley, Zellhoefer, and Marvel (3) and there is no formal difficulty in assuming that any C—H bond can do so, producing hydrogen bonds of a lesser degree of firmness.

Evidently, the solvents which contain more positive hydrogen and hence form stronger hydrogen bonds with the vulnerable oxygen will more effectively block up these vulnerable points, and hence reduce the speed of the above reaction. Taking an example of benzene and hexane, it is known that benzenoid hydrogens are more positive than aliphatic hydrogens, and hence the former will more effectively block up the vulnerable oxygens from attack than does the hexane or heptane and hence we should expect the reaction to be faster in hexane than in benzene. By the same reasoning the speed will be much less in chloroform than in carbon tetrachloride, because chloroform has a polar hydrogen to block up the reactive oxygen, whereas carbon tetrachloride has none. The values for the speed of the above reaction are given in Table I as determined by Soper and Williams (17) and by Menschutkin (9). It will be observed that the data are in the sense expected from theory.

Evidently, the idea can be applied without any ambiguity to simple solvent pairs like benzene and hexane, or chloroform and carbon tetrachloride, or to those solvents which contain essentially only one type of center, but it becomes sometimes a little ambiguous in application to solvents which contain both donor and acceptor groups. However, it is interesting to note that the results with other solvents are not in violation of the above principle.

TABLE I

ESTERIFICATION OF ACETIC ANHYDRIDE

SOLVENT	BY ETHYL ALCOHOL $K_{50°}$ (17)	BY ISOBUTYL ALCOHOL $K_{100°}$ (9)	BY ISOBUTYL ALCOHOL $K_{100°}$ (9)
Hexane	0.0119	0.0877	0.0307
Heptane	.0126		
Carbon tetrachloride	.0113		
Chlorobenzene	.00533		
Xylene	—	.0510	.0196
Benzene	.00462	.0401	.0148
Anisole	.00293		
Chloroform	.00404		
Nitrobenzene	.00245		

Menschutkin reaction. We now discuss a typical organic reaction of the electron pair sharing type, the reaction of a halide with a base. This type of reaction in its various modifications has received the most attention from the viewpoint of solvent effect. In general, the reaction of, say, ethyl iodide with any base, B, can be represented as

$$C_2H_5 : I + : B = [C_2H_5 : B]^+ + [: I]^-$$

i.e., the net effect of any such nucleophilic substitution on carbon is the gain of the electron pair by the covalent iodine atom to form an iodide ion. Let us consider the effect of solvents on the sharing of this electron pair. Strong donor solvents like nitrobenzene will form weak hydrogen bonds with the alkyl CH groups. This donation will be inductively transmitted to the C → : I bond, making the electron pair shift towards iodine. In other words a donor solvent will help the reaction. This mechanism is necessarily very weak and only partly accounts for why the reaction, $C_2H_5I + (C_2H_5)_3N \rightarrow$ runs over 1000 times faster in nitrobenzene and over 200 times faster in anisole than in hexane. The data for this reaction from Menschutkin's (10) classical work and from recent work of other authors (6) are given in Table II, which clearly establishes the above effect of donor solvents. The agreement between the data of Menschutkin and those of Grimm and co-workers is, however, very poor, the discrepancy being 2 to 4 times in all cases where data exist, and so we shall only put reliance on these figures as far as the order of speed in different solvents goes, and not in their absolute values.

TABLE II

KINETICS OF THE REACTION $(C_2H_5)_3N + C_2H_5I \rightarrow (C_2H_5)_4N^+I^-$ IN VARIOUS SOLVENTS AT 100°

SOLVENT	k_2 (10)	k_2 (6)
Hexane	0.00018	0.0003
Cyclohexane		.0006
Heptane	.00023	
Toluene		.0152
Benzene	.00584	.0239
Xylene	.00287	
Chlorobenzene	.0231	.0827
Bromobenzene	.0270	.0959
Iodobenzene		.1590
o-Dichlorobenzene		.150
m-Dichlorobenzene		.0665
p-Dichlorobenzene		.042
Benzonitrile		.673
Nitrobenzene		.830
Anisole	.0403	
Acetone	.0608	
Acetophenone	.1294	
Methyl alcohol	.0516	
Ethyl alcohol	.0366	
Benzyl alcohol	.133	

We are not in a position to compare two hydrocarbons, such as hexane and benzene, on the above consideration alone, because our present knowledge is not sufficient to tell how the electron pair in question will be affected by van der Waals forces between the alkyl group and the hydrocarbon solvent. Fortunately, however, we can approach the problem in this case in another way, since other forces stronger than van der Waals forces are operative here and have more influence in the matter. Since iodide ion is a base in the Lewis sense, the hydrogen in the solvent will tend to function, though very weakly, as acceptor from iodine at the iodine end as shown below:

$$C_2H_5 \;:\overset{\cdot\cdot}{\underset{\cdot\cdot}{I}}: \;\dashrightarrow\; \underset{\text{Solvent}}{H\text{—}C} \quad \text{(arrow shows donation tendency)}$$

Evidently the more electrophilic or polar is this hydrogen, the stronger will be this disruptive influence on iodine and so higher the speed. Hence, benzene will be more powerful than hexane and similarly for other solvents. This is in complete accord with the data for the above reaction in Table II.

Similarly, we expect chloroform to produce higher speed than carbon tetrachloride; we do not have data to the point from Menschutkin but this is confirmed by the data from Norris and Prentiss (11) (see Table IV) on a similar reaction between pyridine and methyl iodide. This idea of higher speed caused by electrophilic centers for this reaction accounts for the high speed in alcohols whose hydroxylic hydrogen is undoubtedly a better hydrogen bonding or electrophilic center than a hydrogen in a C—H bond. An evident consequence is that the reaction speed will vary in the order primary > secondary > tertiary, since the acidity or polarity of the hydroxylic hydrogen varies in the above order. We have no available data to test this point.

We might point out that of the above two mechanisms suggested for the enhancement of speed, *viz.*, (a) by the donor property of oxygen acting on the weakly electrophilic alkyl hydrogen, and (b) by the acceptor or electrophilic property of the solvent hydrogens acting on the iodine, we do not know for certain which one has a stronger effect. The fact, that all the donor solvents which can also act as acceptors produce much higher speed than that in ether, which can function only as a donor, suggests that mechanism b is much more important than mechanism a in enhancing the reaction speed. It should also be pointed out here that these solvent effects will also act on the base used in the above reaction, but that they will have negligible effect on the reaction speed in this case, because these bases are strong enough (primary base in the Lewis sense) to require no energy of activation in any solvent to react with an acid, particularly a strong acid of the carbonium type.

DISCUSSION

Basic principle. We might now attempt to express the above concept in a more formal and succinct way, but before doing so it might be well to review the basic ideas which we have built upon. We have made free use of three different current ideas. First, we have accepted the electronic mechanisms as envisaged by organic chemists following the cue from the Lewis theory. Second, we have accepted the idea of hydrogen bonding taking place between any positive hydrogen and any negative element present in the system. Third, we have extended the latter idea so that all hydrogens, including even those in the alkanes, can take part in hydrogen bonding process; the strength of the hydrogen bond will depend on the polarity of the C—H bond, and hence these bonds will certainly be extremely weak with hydrocarbons but will differ greatly among themselves.

We can now formulate the basic principle we have utilized, thus: *The more a solvent blocks up by hydrogen bond or otherwise the active centers which take part in a chemical reaction, the less will be the speed in it; the more a solvent, by suitable hydrogen bond or otherwise, helps electron shift necessary to the reaction, the higher will be the speed in the solvent.*

An interesting consequence of the above principle is that if a reaction consists of a direct attack of an electrophilic center by a nucleophilic center, say a hydrogen atom in a molecule by an oxygen, the speed will be maximum in an inactive solvent, and the introduction of any electrophilic or electrodotic group in the solvent will retard the reaction. Besides our first case which illustrates this type of behavior, another very apt illustration of this mechanism is the photochemical oxidation of chloroform by oxygen investigated by Plotnikov (13). It will be observed from his data (Table III) that the speed is the highest in CCl_4, hexane, etc., and any increase of acidic or basic tendency in the solvent molecule reduces the speed by blocking off the active centers of reaction.

In attempting to apply the above concepts to some more known cases, it is surprising and regrettable that reliable and systematic data exist for very few uncatalyzed reactions of any other type. Most organic reactions studied with regard to solvent effect are either of the Menschutkin type or esterification type and the same kind of solvent effect persists in practically all of them, as was noticed in as early as 1912 by Patterson and Montgomerie (12) who remarked, "it appears that solvents influence quite different reactions in a uniform manner; although the manifestation of this effect may be of an opposite character, a given set of solvents may hasten a particular reaction in a certain sequence, whilst in the same or very nearly the same sequence they retard another reaction." That this is true on the Menschutkin type reaction is shown by the data in Table IV, collected from various authors. There is one interesting point to note from Table IV.

TABLE III

RELATIVE REACTION VELOCITY OF THE PHOTOCHEMICAL OXIDATION OF IODOFORM IN VARIOUS SOLVENTS

SOLVENT	RELATIVE RATE
Carbon tetrachloride	39.4
Benzene	34.6
Carbon disulfide	24.1
Ether	17.0
Ethyl acetate	8.1
Methyl alcohol	3.2
Ethyl alcohol	2.3
Acetone	0.7

Data from Plotnikov (13).

$$\text{(a) } RCOCH_2{:}Br + \text{Base} = Br^- + [RCOCH_2{:}\ \text{Base}]^+$$
$$\text{(b) } RCH_2CH_2{:}Br + \text{Base} = Br^- + [RCH_2CH_2{:}\ \text{Base}]^+$$

It follows from our theory that if we have two reactions, (a) and (b), in two solvents, say hexane and benzene, the increment in speed for reaction (a) will be much less than that for reaction (b) because the increased polarity of benzene will no doubt enhance the speed by acting through mechanism II at the bromide end, but will also retard the speed by attaching itself more firmly on the keto oxygen and hence tend to oppose the electron shift necessary for the reaction. Therefore the rate of increase of speed with increasing electrophilic nature of the solvent will be less for (a) than for (b). In other words, we deduce the relation

$$\frac{(K_a)\text{ active solvent}}{(K_a)\text{ hexane}} < \frac{(K_b)\text{ active solvent}}{(K_b)\text{ hexane}}$$

where K_a and K_b are the speeds of the reaction (a) and (b) respectively and active solvent means any solvent which has more electrophilic hydrogen than hexane.

TABLE IV

SOLVENT EFFECT ON REACTION SPEED

SOLVENT	1	2	3	4	5	6	7
Hexane	0.0018			0.00014			
Ethyl ether	.00063	0.000607		.00025			
Isopropyl ether						1.195	
Ethyl acetate	.0223			.0108			
Carbon tetrachloride						1.65	0.00002
Toluene			.000231		0.00126	2.07	
Benzene	.00584	.000644	.000305	.0024	00223	2.15	
Chloroform		.000970				2.525	.000434
Chlorobenzene	.0231					2.60	
Anisole	.0403			.0160		2.83	.000886
Nitrobenzene		00617	.0129	.150	0848	3.57	.0048
Acetone	0608	.0139	.00505	.071	.0338		
Benzyl alcohol	.133	.0208		.042			

1$K_{100°}$ for $C_2H_5I + (C_2H_5)_3N \rightarrow$; Menschutkin (10).

2$K_{27.8°}$ for $C_6H_5COCH_2Br + C_6H_5NH_2 \rightarrow$; Cox (4).

3$K_{28.8°}$ for $CH_2 = CHCH_2Br + C_5H_5N$(pyridine) $\rightarrow$; Hawkins, *J. Chem. Soc.*, **123**, 1170 (1922)

4$K_{30°}$ for $NO_2C_6H_4CH_2Cl\ (CH_3)_3N \rightarrow$; McCombie, Scarborough and Smith, *J. Chem. Soc.*, 802 (1927).

5$K_{25°}$ for $C_2H_5I + C_5H_5N$(pyridine) $\rightarrow$; Norris and Prentiss (11).

6$K_{100°}$ (calculated) for $CH_3I + C_5H_5N$(pyridine) $\rightarrow$; Pickles and Hinschelwood, *J. Chem. Soc.*, 1353 (1936).

7$K_{60°}$ for $CH_3I + C_5H_5N \rightarrow$; Thompson and Blandon, *J. Chem. Soc.*, 1237 (1933).

We do not have data in the literature to test this with aliphatic compounds, but the data of Cox (4) in column 2, using ω-bromoacetophenone ($C_6H_5COCH_2Br$), show this trend very strikingly when compared to Menschutkin's data using ethyl iodide (C_2H_5I) in column 1. In every case as we go down the column (Table V) the increase of speed with reference to ether is much less in column 1 than in column 2. As reference speed, hexane would have been much better but unfortunately Cox has given no data for hexane and hence we are forced to take the data for ether as reference, since it is known to have speed in the same range as hexane.

There is, however, one basic difficulty in applying our knowledge of solvent acidity or basicity derived from the study of any particular source towards quantitative deduction. Lewis (8) has clearly pointed out that the order of basic strengths for different bases will differ with the acid used for comparison, and there is no fundamental reason to attach any absolute significance to the order of basicities obtained with the proton as the acid. Now, since many organic reactions occur through the intervention of the carbonium ion, which is an acid in the Lewis sense, strictly comparable results can hardly be expected, though the general trend cannot be masked owing to this factor. Furthermore, it is impossible to classify a solvent as purely acidic or purely basic in the Lewis sense, or pure donor or pure acceptor as Sidgwick would prefer to call it, for they not only differ widely among themselves in degree, but most solvents are capable of exercising both functions. This has been pointed out by many authors, for example, by Bell (2) and by Ewell and co-workers (5), and hence it is impossible to generalize the effect of a solvent with respect to its acidity or basicity, and every case requires consideration on its own merit along the lines indicated.

TABLE V

THE RELATIVE SOLVENT EFFECT IN MENSCHUTKIN REACTION OF A HALOGENATED KETONE AND AN ALKYL HALIDE

(a) $C_6H_5COCH_2Br + C_6H_5NH_2 \rightarrow (C_6H_5COCH_2)(C_6H_5)H_2N^+ Br^-$
(b) $CH_3CH_2I + (C_2H_5)_3N \rightarrow (C_2H_5)_4N^+I^-$

SOLVENT	$\frac{(K_a)\text{ solvent}}{(K_a)\text{ ether}}$	$\frac{(K_b)\text{ solvent}}{(K_b)\text{ ether}}$
Ether	1.0	1.0
Benzene	1.06	9.28
Acetone	24.9	96.6
Benzyl alcohol	46.1	211.

be difficult to predict. However, as we have clearly illustrated our concept by the above typical examples, we shall not extend the same to the other rather limited data available.

The difficulty of any generalized treatment can further be appreciated if we remember that most reactions are essentially, as pointed out by Ingold (7), an interaction between an electrophilic center of one molecule and a nucleophilic center of another molecule, and any solvent which will block up one of these centers will tend to activate the other. Therefore, unless one of the centers is strong enough to overrule this intervention by the solvent molecule or weak enough to be unaffected by such influence, small differences between similar solvents might

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[Contribution from the Cobb Chemical Laboratory of the University of Virginia]

ANTIMALARIALS.[1] SOME NEW SECONDARY AND TERTIARY ARYLMETHYLAMINES

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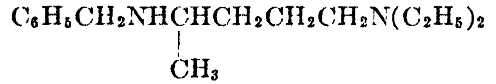
In the course of the investigation of the antimalarial activity of the substituted α-phenyl-β-dialkylaminoethanols (1) attention was given to the evaluation of a variety of substituents on the nitrogen. In this connection a number of new secondary benzylalkylamines were made and used in condensations with nuclear substituted α-bromoacetophenones, especially the para-chloro derivative; these amines, listed in Table I, were made from the corresponding aromatic aldehydes by condensation with the appropriate primary amines to the Schiff bases (a few of which are listed in Table II), and by subsequent hydrogenation with Raney nickel (*cf.* ref. 2–7). One secondary amine, N-(α-butylbenzyl)-methylamine (XII) was made by the addition of butylmagnesium halide to benzalmethylamine.

The N-benzyl derivative of novalamine (XXXVII) and the analogous N-



$$C_6H_5CH_2NH\underset{CH_3}{\underset{|}{C}H}CH_2CH_2CH_2N(C_2H_5)_2$$

XXXVII (SN-3942)[3]

benzyl-N-(3-diethyl- and 3-dibutylaminopropyl)amines, were made for use as secondary amines in the synthesis of amino alcohols; the novalamino compound (XXXVII) was itself tested against avian malaria ($Q = < 0.3$).[4]

A second aspect of the studies in this field was the interest in some of these compounds themselves as possible antimalarials. This interest was stimulated by reports of the slight activity shown by a few individual compounds of this type, for example, benzyltetradecylamine and *p*-methylbenzyldodecylamine (8). This led to the synthesis of the tertiary arylmethyl amines listed in Table III which include six *para*-halogenobenzyl compounds and six α-naphthyl-

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[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

[2] Present locations: [a]University of Texas, Austin, Texas; [b]Chemical Abstracts, Columbus, O.; [c]Smith, Kline and French Lab., Phila., Penna; [d]Southern Research Institute, Birmingham, Ala.; [e]Birmingham-Southern College, Birmingham, Ala; [f]Rohm and Haas Co., Phila., Penna.

[3] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which survey numbers have been assigned have been tabulated in the Monograph (8).

[4] These tests, A-1, as described in the Survey Monograph (8), were carried out at the National Institute of Health under the direction of Dr. G. Robert Coatney.

TABLE I

SECONDARY (ARYLMETHYL)AMINES. $ArCH_2NHR$

	$ArCH_2$-	R-	PREP.[a] METHOD	YIELD %	B.P. C°/MM.	n_D^{20}	M. P. C° HYDRO-CHLORIDE
I	$C_6H_5CH_2$-	*i*-propyl-	DFJ	93	66–68/1	1.5029	195
II	$C_6H_5CH_2$-	*s*-butyl-	AFH	95	84–86/2	1.5023	143–145
III	$C_6H_5CH_2$-	*n*-octyl-	BEG	83	156–157/13	1.5068	—
IV	$C_6H_5CH_2$-	*n*-dodecyl-	DG[b]	70	185–190/2	—	201–202.5
V	$C_6H_5CH_2$- (2,3)	cyclo-hexyl-	CFG[c]	56	209–210/98[h]	$1.5290^{23°}$	252–253
VI	*ortho* $ClC_6H_4CH_2$-	CH_3-	CEJ	—	83–84/2	1.5405[h]	—
VII	*para* $ClC_6H_4CH_2$-	CH_3-	BEJK	85	118–121/23	—	194–195
VIII	*para* $CH_3OC_6H_4CH_2$-	CH_3-(7)	—[d]	75	88–96/2	—	—
IX	*para* $CH_3OC_6H_4CH_2$-	*n*-butyl-	—[e]	82	147–151/2[h]	$1.508^{25°}$	—
X	α-furyl-CH_2-	ethyl-(4,5)	CEG[i]	49	73–75/25	—	120–121
XI	α-naphthyl-CH_2-	CH_3- (6)	—[f]	93	—	—	187–188
XII	$C_6H_5CHCH_2CH_2CH_2CH_3$ |	CH_3-	—[g]	61	242–243	—	144–145

[a] The letters indicate conditions and procedures described in the experimental section.

[b] A 0.07-mole run. There was formed a considerable amount of di-*n*-dodecylamine which was isolated and identified.

[c] A small amount (3 ml.) of concentrated ammonium hydroxide was added to the 3-mole reduction mixture.

[d] Reduction was with Raney nickel at about 1400 lbs. per sq. in. at room temperature.

[e] Reduction was with Raney nickel at about 1800 lbs. per sq. in. at 165° (10 hrs.).

[f] Made from α-(chloromethyl)naphthalene (*cf.* Ref. 6). The product was crystallized from isopropanol.

[g] See experimental part.

[h] Not analyzed.

[i] Prepared by James A. Freek.

TABLE II

SCHIFF BASES. $ArCH{=}NR$

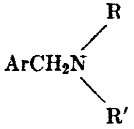
	Ar-	R	B P C°/MM.	n_D^{20}	PREP.[a] METHOD	YIELD %
XIII	C_6H_5-	*i*-propyl-	64/1	—	A	83[b]
XIV	C_6H_5-	*s*-butyl-	86–88/3	1.5211	A	92[b]
XV	C_6H_5-	*n*-octyl-	142–143/2	1.5136	A	85
XVI	C_6H_5-	*n*-dodecyl-	167/1	1.5022	D	80
XVII	*ortho* ClC_6H_4-	CH_3-	78–80/2	1.5660	C	85[b]
XVIII	*para* ClC_6H_4-	CH_3-	69–71/2	—	B	93
XIX	*para* $CH_3OC_6H_4$-	CH_3-	113–115/14	—	B	83[b]
XX	*para* $CH_3OC_6H_4$-	*n*-butyl-	126–127/3.5	—	A	73[b]

[a] The letters refer to the procedures for preparing the Schiff bases, which are outlined in the experimental part.

[b] These compounds were not analyzed, but were reduced directly, to the secondary amines.

TABLE III

TERTIARY (ARYLMETHYL)AMINES.



$ArCH_2N(R)(R')$

	SN	Ar-	R	R'	Q[a]	PREP.[a] METHOD	YIELD[b] %	B.P.C°/MM.	n_D^{20}	M.P HYDRO-CHLORIDE
XXI	7110	C_6H_5-	$C_6H_5CH_2$-	*n*-decyl-	<0.03	H	—	216–217/0.5	1.5253	—
XXII	7518	C_6H_5-	$C_6H_5CH_2$-	myristyl-	<0.03	I	—	216–217/2	1.5130	—
XXIII	7916	C_6H_5-	$C_6H_5CH_2$-	$C_6H_5CH_2CH_2$-	<0.03	J	72	—	—	201–203
XXIV	7111	*p*-ClC_6H_4-	*n*-octyl-	*n*-octyl-	0.06	BD	—	225–226/0.5	1.4903	—
XXV	7516	*p*-ClC_6H_4-	*n*-nonyl-	*n*-nonyl-	<0.03	BD	—	234–235.5/0.5	1.4889	—
XXVI	7515	*p*-ClC_6H_4-	-N-tetrahydroquinolyl-		<0.06	BE	73	—	—	54–55[c]
XXVII	7919	*p*-BrC_6H_4-	*n*-octyl-	*n*-octyl-	0.03+	BD	—	228–229/0.5	1.5003	—
XXVIII	6549	*p*-BrC_6H_4-	$C_6H_5CH_2$-	cyclohexyl-	<0.06	AE	65	—	—	67–68[c]
XXIX	8115	*p*-BrC_6H_4-	*p*-$CH_3OC_6H_4CH_2$-	*n*-butyl-	<0.03	BD	—	215.5/0.5	1.5629	—
XXX	6972	*p*-BrC_6H_4-	$C_6H_5CH_2$-	$C_6H_5CH_2$-	<0.03	BG	52	—	—	203–204[d]
XXXI	7987	α-naphthyl-	ethyl-	ethyl-	<0.08	BDG[f]	48	—	—	217–218
XXXII	8344	α-naphthyl-	*n*-amyl-	*n*-amyl-	<0.06	BDF[g]	57	187–188/1	1.5395	—
XXXIII	7986	α-naphthyl-	$C_6H_5CH_2$-	CH_3-(6)	<0.03	BCG[f]	96	—	—	223–225[e]
XXXIV	8116	α-naphthyl-	$C_6H_5CH_2$-	$C_6H_5CH_2$-	<0.03	BDG[g]	80	—	—	192–194
XXXV	7521	α-naphthyl-	*p*-$ClC_6H_4CH_2$-	CH_3-	<0.03	BDG[f]	—[h]	—	—	208–209
XXXVI	8476	α-naphthyl-	*p*-$CH_3OC_6H_4CH_2$-	CH_3-	<0.03	—[f,i]	87	—	—	188–190

[a] See experimental part under the heading "The arylmethyl tertiary amines."

[b] Of good material but not necessarily brought to analytical purity.

[c] Melting point of the base.

[d] The base melts about at room temperature; it was filtered (cold) and converted into the hydrochloride.

[e] B and B. (6), 225°.

[f] From α-(chloromethyl)naphthalene.

[g] From α-(bromomethyl)naphthalene.

[h] The yield was nearly quantitative.

[i] No solvent was used. Reaction occurred quickly with temperature rise, and after standing, cooling, digesting with ether, and filtering off the secondary amine hydrochloride, the product was isolated from the filtrate.

methyl derivatives; the molecular weight in each case was brought to a fairly high level by means of appropriate alkyl groups on the nitrogen. The introduction of halogens into the phenyl nucleus was expected to increase activity as it does in so many other types (8), and the choice of the α- rather than the β-naphthyl series was based on the higher antimalarial activities of the corresponding α-naphthyl amino alcohols (9).

The preparation of the tertiary amines involving at least one arylmethyl group was usually accomplished by the action of the appropriate arylmethyl halide on an available secondary amine, using in some cases a secondary arylmethylamine from Table I. In the synthesis of the α-naphthylmethyl compounds, naphthalene was chloromethylated by a variation of the Darzens and Lévy method (10). It was found impractical to use unpurified material, however, since the condensation with secondary amines was slow and apparently allowed secondary reactions to interfere seriously. The more reactive bromomethyl compound was made by the hydrobromic-acetic acid method (11), and much better results were achieved in these condensations.

The results of screening tests against avian malaria were disappointing in that only two compounds showed slight activity against *gallinaceum* in the chick (8). *p*-Chlorobenzyldioctylamine showed Q = 0.06 as compared with the Q = 0.25 in the case of α-(4-chlorophenyl)-β-dioctylaminoethanol (1).

EXPERIMENTAL[5, 6]

The Schiff bases in most cases (A) were made by adding the primary amine dropwise with stirring into benzaldehyde or the appropriate derivative, with continued stirring for at least 4–24 hours, separating from the water formed, and fractionally distilling the product under reduced pressure. In a few cases (B) a cooled mixture of benzene, the aldehyde, and primary amine hydrochloride was treated dropwise with a slight excess of the calculated amount of concentrated sodium hydroxide, and allowed to stand for two hours. In one case (C) a 25% aqueous methylamine solution was used (overnight). Often the Schiff base thus obtained was not further purified or characterized and was used directly in the reduction to the secondary amine. In one case (D) the condensation was run in ether as the solvent to dissolve the reactants (one hour).

Hydrogenation of the Schiff bases. (For literature, see Ref. 12). Raney nickel was used as catalyst and hydrogenation was usually run at room temperature and atmospheric pressure. In some cases (A) no solvent was used, and in others 95% ethanol, in (B) the very small amounts necessary for introduction of the catalyst, or in larger amounts (C) on the order of 1–2 volumes. In one case a small amount of absolute ethanol was used (D). The reductions were usually slow when the reduction was run in (E) one molar or (F) larger scale. Some reductions (G) required 12–24 hours for absorption of the calculated amount of hydrogen, others required longer, from (H) two or three days, to (I) five days, or longer (J). The products were always fractionally distilled under reduced pressure, and in some cases were then converted into the hydrochlorides.

It is interesting to note that Raney nickel caused elimination of only a very small amount of the *para* halogen, as was shown in the case of 4-chlorobenzylmethylamine, where after one typical reduction (K) an aliquot portion of the solution was treated with silver nitrate

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[5] All melting points are corrected.

[6] A number of the microanalyses were carried out by Misses C. H. Vondra, Geraldine Alley and Mrs. Joyce B. Caliga.

and the resulting precipitate of silver halide was filtered and determined quantitatively; this demonstrated that reductive elimination of the *para* chlorine had occurred to the extent of 3.8%.

N-(1-Phenylpentyl)methylamine (XII). (*cf.* Ref. 13). A solution of 0.444 mole of *n*-butylmagnesium bromide in 300 ml. of absolute ether and 300 ml. of toluene was distilled until the temperature of the residual mixture reached 100°; 37.4 g. (0.314 mole) of benzalmethylamine in an equal volume of toluene was added over fifteen minutes with refluxing, and refluxing was continued for an additional fifteen minutes. Upon hydrolysis, extraction with ether, and drying over sodium sulfate with Norit treatment, the oil which was obtained was distilled under reduced pressure; 34.6 g. (61%); b.p. at atmospheric pressure, 242–243°. It was converted into the hydrochloride from ether.

TABLE IV

ANALYSES

	EMPIRICAL FORMULA	CRYSTALLIZED FROM	CALC'D C(N)	FOUND C(N)	CALC'D H	FOUND H
I	$C_{10}H_{15}N$	—	[N]9.39	9.47	—	—
	$C_{10}H_{15}N\cdot HCl$	isopropanol	64.68	64.58	8.68	8.39
II	$C_{11}H_{17}N$	—	[N]8.58	8.53	—	—
	$C_{11}H_{17}N\cdot HCl$	butanone	[N]7.01	7.25	—	—
III	$C_{15}H_{25}N$	—	82.13	81.86	11.49	11.58
IV	$C_{19}H_{33}N\cdot HCl$	—	[N]4.49	4.37	—	—
VII	$C_{8}H_{10}ClN\cdot HCl$	ether[a]	[N]7.29	7.19	—	—
XII	$C_{12}H_{19}N\cdot HCl$	ether-EtOH	[N]6.56	6.43	—	—
XV	$C_{15}H_{23}N$	—	82.89	83.25	10.66	10.33
XVI	$C_{19}H_{33}N$	—	[N]5.12	4.90	—	—
XVIII	$C_{8}H_{8}ClN$	—	[N]9.12	8.74	—	—
XXI	$C_{24}H_{35}N$	—	[N]4.15	4.09	—	—
XXII	$C_{28}H_{43}N$	—	[N]3.56	3.64	—	—
XXIII	$C_{22}H_{23}N\cdot HCl$	EtOH-ether	[N]4.15	4.41	—	—
XXIV	$C_{23}H_{40}ClN$	—	[N]3.83	3.84	—	—
XXV	$C_{25}H_{44}ClN$	—	[N]3.55	3.84	—	—
XXVI	$C_{16}H_{16}ClN$	isopropanol	[N]5.43	5.38	—	—
XXVII	$C_{23}H_{40}BrN$	—	[N]3.41	3.53	—	—
XXVIII	$C_{20}H_{24}BrN$	ethanol	[N]3.91	4.30	—	—
XXIX	$C_{19}H_{24}BrNO$	—	62.98	62.98	6.68	6.79
XXX	$C_{21}H_{20}BrN\cdot HCl$	abs. EtOH	[N]3.48	3.46	—	—
XXXI	$C_{15}H_{19}N\cdot HCl$	CH_3OH-ether	72.12	72.44	8.07	7.73
XXXII	$C_{21}H_{31}N$	—	[N]4.71	4.94	—	—
XXXIV	$C_{25}H_{23}N\cdot HCl$	isopropanol	[N]3.75	3.96	—	—
XXXV	$C_{19}H_{18}ClN\cdot HCl$	isopropanol	[N]4.22	4.34	—	—
XXXVI	$C_{20}H_{21}NO\cdot HCl$	acetone-ether	[N]4.27	4.54	—	—

[a] Precipitated from ether by ethereal hydrogen chloride.

[N] Those analyses carrying this designation are for nitrogen.

The arylmethyl tertiary amines were made by the interaction of one equivalent of the arylmethyl- or alkyl-halide and two equivalents of the appropriate secondary amine in (A) benzene or (B) ether as solvent, either with refluxing (C) until the precipitation of the halogen as the secondary amine hydrohalide was complete (10–15 hours), or allowing the mixture to stand for a much longer time at room temperature (D). The secondary amine hydrochloride was filtered off and served as indication of the progress and completion of the reaction. Evaporation of the solvent gave the tertiary amine which, if it was a solid, was crystallized (E), or, if not, was distilled (F), or converted into the hydrochloride (G).

In the case of the benzylamine condensations with (H) decyl and (I) myristyl iodides the reactions were run in xylene under refluxing for two hours. In one case (J) the product was obtained by the interaction of a 2:1:2 equivalent mixture of benzyl bromide, β-phenylethylamine, and aqueous sodium carbonate with shaking for twenty-four hours (the crude base in this case boiled at 206–211° at 3 mm.).

α-(Bromomethyl)naphthalene was made by a modification of the method of Darzens and Lévy (10, 11) using 30% hydrogen bromide in concentrated acetic acid. Naphthalene (130 g.) was added with stirring to a solution of 40 g. of paraformaldehyde in 400 ml. of 30% hydrobromic-acetic acids and the mixture was heated for eighteen hours at 55°. Extraction with benzene and washing with sodium carbonate and with water, drying, and distilling, gave a cut of 123 g. (55%) boiling at 150–155° (1 mm.); it crystallized upon cooling.

N-Benzyl-N-(4-diethylaminopentyl)amine (XXXVII) was made by allowing 68.4 g. (0.4 mole) of benzyl bromide to react with 126 g. (0.8 mole) of novalamine in 200 ml. of ether. The ether solution was decanted from the resinous precipitate of hydrobromides, was washed with water, dried, and evaporated. The oil thus obtained, on fractional distillation at 4.5 mm., gave cuts totaling 46 g. of boiling range 142.5–149° and n_D^{30} 1.4982–1.4989. The dihydrochloride was precipitated from ether (with decantation of this solvent) and crystallized several times from absolute ethanol; hygroscopic; softens at 85–87° and melts at 142–144°.

Anal. Calc'd for $C_{16}H_{28}N_2 \cdot 2HCl$: C, 59.80; H, 9.41; Cl^-, 22.07.
Found: C, 59.00; H, 9.32; Cl^-, 21.91.

In a second preparation, benzaldehyde was condensed with novalamine (Procedure A) and the Schiff base, N-benzal-N-(4-diethylaminopentyl)amine, was obtained as an oil [b.p. 155.5° (14 mm.); n_D^{20} 1.5180] (not analyzed), and was hydrogenated to the secondary amine with Raney nickel (Procedure B); this product was identified as the dihydrochloride.

N-Benzyl-N-(3-di-n-butylaminopropyl)amine. The crude Schiff base obtained by allowing an equimolar mixture of benzaldehyde and γ-dibutylaminopropylamine to stand overnight, separating from water generated, and washing with saturated sodium chloride solution, was hydrogenated with Raney nickel (Procedure B); yield 39%; redistillation gave a boiling range of 169–170° (6 mm.); n_D^{23} 1.4920–1.4923.

Anal. Calc'd for $C_{18}H_{32}N_2$: N, 10.13. Found: N, 10.21.

N-Benzyl-N-(3-diethylaminopropyl)amine was made by condensing 53 g. of benzaldehyde with 65 g. of γ-diethylaminopropylamine (shaking overnight), separating from the water generated, and hydrogenating with Raney nickel at 100° and a pressure of 1900 lbs. per sq. in. Fractionation at 4 mm. pressure gave 62.5 g. of product boiling at 132–134°. Redistillation gave the boiling point 129° (3.5 mm.); n_D^{25} 1.5010.

Anal. Calc'd for $C_{14}H_{24}N_2$: N, 12.72 Found: N, 12.99.

SUMMARY

Eight new arylmethyl secondary amines have been synthesized by Raney nickel hydrogenation of Schiff bases, for use in the synthesis of α-dialkylaminomethylbenzyl alcohols.

Three N-benzyl-N-(dialkylaminoalkyl)amines are reported.

Fifteen new arylmethyl tertiary amines were made from primary and secondary amines by condensation with arylmethyl or alkyl halides; these were made for the purpose of antimalarial tests.

CHARLOTTESVILLE, VIRGINIA

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF
THE UNIVERSITY OF VIRGINIA]

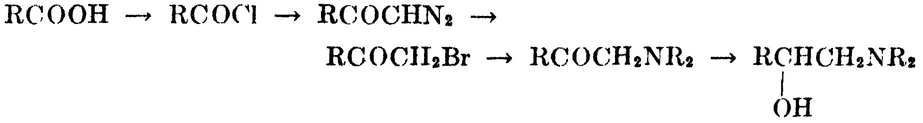
ANTIMALARIALS.[1] ALIPHATIC AMINO KETONES AND ALCOHOLS

ROBERT E. LUTZ AND JAMES W. WILSON, III[2]

Received January 6, 1947

The synthesis of a variety of aliphatic amino ketones and alcohols was initiated in 1942 in order to explore the field for possible antimalarial drugs, and to evaluate the effectiveness in this respect of the β-aminoethanol grouping, either in a completely aliphatic system or separated from an aryl group by at least one intervening methylene group. The work was soon discontinued however because the few compounds made proved to be without significant activity (1). These compounds are being reported for comparison with the α-aryl-β-aminoethanols listed in a preceding paper (2) and with the di-(amino alcohols) described in a following paper (3). The investigations in this field were anticipated in part in two papers by Work (4, 5).

The amino ketones were made from the aliphatic acids, lauric, stearic, cyclohexane carboxylic, and diphenylacetic, by way of the following steps: conversion to the acid chlorides, diazomethylation, hydrobromination to the bromo ketones, and condensation with the appropriate secondary amines. The amino ketones were reduced catalytically or by aluminum isopropoxide to the amino alcohols.



$$\mathrm{RCOOH} \rightarrow \mathrm{RCOCl} \rightarrow \mathrm{RCOCHN_2} \rightarrow \mathrm{RCOCH_2Br} \rightarrow \mathrm{RCOCH_2NR_2} \rightarrow \mathrm{R\underset{OH}{\underset{|}{C}}HCH_2NR_2}$$

The new compounds obtained and characterized are listed in the table.

The results of screening tests against *gallinaceum* in the chick showed most of these compounds to be without significant antimalarial activity; however, it is probable that this field has not had an adequate trial, because the number of compounds made is very small, and because in most cases the choice of substituents on nitrogen has probably not been the optimum, judging from the extensive subsequent results in the α-phenyl-β-dialkylaminoethanol series which are described in a preceding paper (2). It is hoped that some further representatives of this series may still be made.

EXPERIMENTAL[4]

1-Bromotridecanone-2. A solution of 60 g. (1.43 mole) of diazomethane in 2 l. of dry ether (0°) was treated with 104 g. (0.477 mole) of lauroyl chloride [b.p. 184–188° (100 mm.)] in 150 ml of dry ether by dropwise addition over 3 hours under stirring, and was allowed to stand overnight. A solution of 235 g. (1.22 moles) of 42% hydrobromic acid in 200 ml. of ether was added slowly with continuous stirring over 4 hours, with the temperature maintained at 18°. Upon standing at room temperature for 8 hours and cooling to 0°, the white bromomethyl ketone separated; 95 g.; m.p. 50–52°; second crop, 26 g.; m.p. 48.5–50°; total yield 92%. Repeated crystallization from ethanol brought the melting point to 53°.

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[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

[2] Present address: Smith, Kline and French Laboratories, Philadelphia, Pa.

[4] All melting points are corrected.

Anal. Calc'd for $C_{13}H_{25}BrO$: C, 56.31; H, 9.00.

Found: C, 56.00; H, 8.84.

1-N-(Diethylamino)tridecanone-2 hydrochloride (I). Diethylamine hydrobromide precipitated immediately in 95% yield upon slow addition with stirring of 21 g. (0.274 mole) of diethylamine to a solution of 30 g. (0.11 mole) of 1-bromotridecanone-2 in 300 ml. of absolute ether. After washing out the excess diethylamine with water, the ether was evaporated and the residual oil was dissolved in dry acetone and neutralized (to Congo) with ethereal hydrogen chloride. The crystalline precipitate was recrystallized from acetone; 18 g. (54.5%); m.p. 73–73°. A mixture melting point with the hydrochloride of I showed a significant depression.

TABLE I

AMINO KETONES AND ALCOHOLS

	SN[3]	FORMULA
I	1627	$CH_3(CH_2)_{10}$-CO-CH_2-N$(C_2H_5)_2$
II	2014	$CH_3(CH_2)_{10}$-CHOH-$CH_2N(C_2H_5)_2$
III	2596	$CH_3(CH_2)_{10}$-CO-CH_2-morpholinyl
IV	2595	$CH_3(CH_2)_{10}$-CHOH-CH_2-morpholinyl
V	8083	$CH_3(CH_2)_{16}$-CO-CH_2-piperidyl
VI	—	Cyclohexyl-CHOH-CH_2N(n-amyl)$_2$
VII	—	$(C_6H_5)_2$CH-CO-CH_2-N$(C_2H_5)_2$
VIII	3263	$(C_6H_5)_2$CH-CHOH-CH_2-N$(C_2H_5)_2$
IX	2743	$(C_6H_5)_2$CH-CO-CH_2-morpholinyl
X	3264	$(C_6H_5)_2$CH-CHOH-CH_2-morpholinyl

Anal. Calc'd for $C_{17}H_{35}NO \cdot HCl$: C, 66.74; H, 11.86; N, 4.58.

Found: C, 66.08; H, 11.90; N, 4.15. (The compound was very hygroscopic).

1-N-(Diethylamino)tridecanol 2 hydrochloride (II). Catalytic reduction of 15 g. of the hydrochloride of I in 300 ml. of 95% ethanol with 0.25 g. of platinum oxide proceeded in 6 hours and stopped with absorption of one molecule of hydrogen Evaporation, addition of water and addition of sodium carbonate precipitated the oily base which was converted into the hydrochloride from dry acetone by ethereal hydrogen chloride; it was recrystallized from acetone; 12 g. (80%); m.p 76–78°.

Anal. Calc'd for $C_{17}H_{37}NO \cdot HCl$: C, 66.30; H, 12.44; N, 4 55.

Found: C, 66.52; H, 12.20; N, 4.31.

1-N-Morpholinotridecanone-2 hydrochloride (III), made like I, was recrystallized from benzene; yield 39%; m.p. 126–127°.

Anal Calc'd for $C_{17}H_{33}NO_2 \cdot HCl$: N, 4.38. Found· N, 4.31.

1-N-Morpholinotridecanol-2 hydrochloride (IV) was obtained by hydrogenation of the amino ketone hydrochloride in the same way as II except that the bulk of the alcohol was evaporated under reduced pressure until the hydrochloride began to precipitate: addition of absolute ether gave 14 g. of the salt (82.5%); m.p. 145–147°. Two crystallizations from butanone brought the melting point to 149–150°.

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[3] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which the Survey Numbers have been assigned have been tabulated in the monograph (1).

Anal. Calc'd for $C_{17}H_{35}NO_2 \cdot HCl$: C, 63.42; H, 11.27.
Found: C, 63.35; H, 11.19.

1-Bromononadecanone-2. Ninety-two grams of stearic acid was converted into the acid chloride by treatment with 60 g. of thionyl chloride and evaporation of the excess reagent under reduced pressure. The crude product (97 g.) was dissolved in 100 ml. of absolute ether and added under stirring to 50 g. of diazomethane in 1500 ml. of absolute ether over 3.5 hrs. at 5°, and the mixture was allowed to stand overnight at room temperature. A solution of 150 g. of 42% hydrobromic acid in 100 ml. of ether was added slowly under stirring; after standing 3 hrs. the volume of solvent was reduced to 300 ml. by distilling, and the bromo ketone separated on cooling to 0°; 100 g. (86.5%); m.p. 69–72°. A second crop of 10 g. was obtained (m.p. 63–66°). Two crystallizations from acetone and two from isopropanol brought the melting point to 70–72°.

Anal. Calc'd for $C_{19}H_{37}BrO$: C, 63.17; H, 10.36.
Found: C, 63.32; H, 10.67.

1-(N-Piperidyl)nonadecanone-2 hydrochloride (V). The reaction between 20 g. (0.055 mole) of crude bromo ketone and 14.1 g. (0.166 mole) of piperidine in 300 ml. of absolute ether proceeded rapidly, and after 0.5 hr. at room temperature, 9 g. of piperidine hydrobromide had separated (98%). Evaporation of the solvent and washing gave a crude solid of m.p. 39–45° which was converted into the hydrochloride in absolute ether; this was crystallized from a 1:9 methanol-acetone mixture; 7.5 g. (57%); m.p. 111–113°.

Anal. Calc'd for $C_{24}H_{47}NO \cdot HCl$: C, 71.68; H, 12.03.
Found: C, 71.55; H, 12.25.

α-Cyclohexyl-β-di-n-amylaminoethanol (VI). Cyclohexane carboxylic acid (100 g.) was converted in the usual way by thionyl chloride into the acid chloride which distilled at 184–188° under 755 mm.; yield 103 g. (91%). Sixty-eight grams of this in 150 ml. of absolute ether was added slowly with stirring over 4 hrs. to 68 g. of diazomethane in 2 l. of absolute ether (0 to −5°); after standing overnight, 190 g. of 42% hydrobromic acid in 200 ml. of ether was added over 3 hrs. at 180° under vigorous stirring. The ether solution was washed with water to remove hydrogen bromide and was evaporated. Half of the residual crude oily bromomethyl ketone was added to an ether solution of 85 g. of diamylamine; the reaction proceeded rapidly and after 1.5 hrs. a 96% yield of diamylamine hydrobromide had separated. The crude amino ketone (oil) was treated with 400 ml. of 1.9 *N* aluminum isopropoxide (refluxing for 4 hrs.) and the product was isolated in the usual way as an oil. It was fractionated and the cut of b.p. 161–170° (2 mm.); n_D^{25} 1.4631–1 4632, was analyzed.

Anal. Calc'd for $C_{18}H_{37}NO$: C, 76.26, H, 13.16.
Found: C, 76.44; H, 12.98.

1-N-Diethylamino-3,3-diphenylpropanone-2 hydrochloride (VII). Diphenylacetyl chloride (5) [113 g. (0.49 mole)] in 400 ml. of absolute ether was added under stirring over 2 hrs. to 60 g. (1.43 mole) of diazomethane in 2 l. of absolute ether (cooled in ice-salt), and the mixture after standing overnight at room temperature was cooled in ice and treated dropwise over 4 hrs. under stirring with 200 g. (1.04 moles) of 42% hydrobromic acid in 100 ml. of ether. Upon concentrating and cooling, the bromomethyl ketone crystallized and was recrystallized from ligroin; 100 g. (78%); m.p. 48–52°. Three crystallizations from isopropanol brought the melting point to 69–70°. This material gave good results in the next steps but analytical results for carbon ran consistently over 1% high.

Treatment of the bromomethyl ketone in absolute ether with diethylamine in the usual way gave an oil which crystallized as the hydrochloride from acetone upon the addition of ethereal hydrogen chloride; yield 45%; m.p. 184–187° decomp. Two crystallizations from isopropanol and one from a 1:4 methanol-acetone mixture gave a product melting at 187–188°.

Anal. Calc'd for $C_{19}H_{23}NO \cdot HCl$: N, 4.41. Found: N, 4.39.

1-N-Diethylamino-3,3-diphenylpropanol-2 hydrochloride (VIII). Reduction of 14.3 g. of the amino ketone in 300 ml. of 95% ethanol using 0.33 g. of platinum oxide went to completion rapidly and stopped afrer absorption of one molecule of hydrogen. The oil obtained was dissolved in isopropanol and crystallized as the hydrochloride upon adding ethereal hydrogen chloride till acid to Congo; 9 g. (62.5%); m.p. 158–159°. Repeated recrystallizations from isopropanol brought the melting point to 161–162°.

Anal. Calc'd for $C_{19}H_{25}NO \cdot HCl$: C, 71.34; H, 8.19.
Found: C, 71.52; H, 8.54.

3,3-Diphenyl-1-(N-morpholinyl)propiophenone-2 hydrochloride (IX) was prepared like VII; yield 52%; m.p. 215–218° decomp. One crystallization from 3:7 methanol-acetone and one from 1:9 methanol-isopropanol mixture raised the melting point to 224–225° decomp.

Anal. Calc'd for $C_{19}H_{21}NO_2 \cdot HCl$: N, 4.22. Found: N, 3.85.

3,3-Diphenyl-1-(N-morpholinyl)propanol-2 hydrochloride (X) was prepared like VIII in 88% yield and recrystallized from ethanol; m.p. 185–186°.

Anal. Calc'd for $C_{19}H_{23}NO_2 \cdot HCl$: C, 68.35; H, 7.25.
Found: C, 68.63; H, 7.38.

SUMMARY

Five new aliphatic α-amino ketones and five β-aminoethanols have been synthesized for antimalarial testing. These were made from lauric, stearic, cyclohexane carboxylic and diphenylacetic acids through diazomethylation of the acid chlorides, hydrobromination and condensation with the appropriate secondary amines. The amino alcohols were made from the amino ketones by catalytic or aluminum isopropoxide reductions.

CHARLOTTESVILLE, VIRGINIA

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF
THE UNIVERSITY OF VIRGINIA

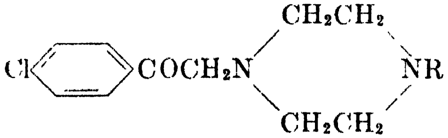
ANTIMALARIALS.[1] SOME PIPERAZINE DERIVATIVES

ROBERT E. LUTZ AND NEWTON H. SHEARER[2]

Received January 6, 1947

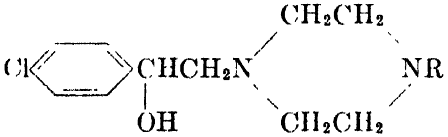
In varying the *tert.*-amino group of the α-aryl-β-aminoethanols which were being made for screening tests against avian malaria (1, 2), it seemed of interest to evaluate the piperazyl group and to compare it on the one hand with the piperidyl group and on the other with dialkylaminoalkylamino groups. Three types of compounds have been prepared, namely: (a) two mono-N-alkylpiperazylmethyl ketones and the two corresponding alcohols (I–IV), (b) several bis-compounds which are di-(amino ketones) and di-(amino alcohols) (V–X), and (c) a few N,N′-dialkyl piperazines (XI–XII), made because at the time (1943) slight antimalarial activity had been reported in the case of a few high molecular weight secondary and tertiary amines (1).

The mono-N-alkylated β-piperazylethanols were prepared by condensing 4-chlorophenacyl bromide with mono-N-amyl and mono-N-benzylpiperazines to produce respectively the amino ketones I and II, and by reducing these compounds by means of aluminum isopropoxide to the amino alcohols, III and IV.



I R = *n*-amyl SN[3]-8415 Q[4] = <0.3

II R = benzyl SN-8121 Q = 0.15



III R = *n*-amyl SN-8782 Q = <0.15

IV R = benzyl SN-8348 Q = <0.1

Two piperazyl diketones (V and VI) were made by condensing phenacyl and *p*-chlorophenacyl bromides directly with piperazine, and one typical piperazyl-dialcohol was made by reduction of VI with aluminum isopropoxide.

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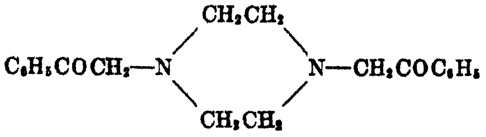
[1] A portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

[2] Present address, Eastman Kodak Co., Rochester, N. Y.

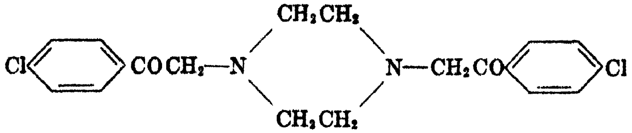
[3] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned have been tabulated in the monograph (1).

[4] Q = quinine equivalents against *gallinaceum* in the chick, as listed in the Survey Monograph (1) and designated as the A-1 test. These results were obtained at the National Institute of Health under the direction of Dr. G. Robert Coatney.



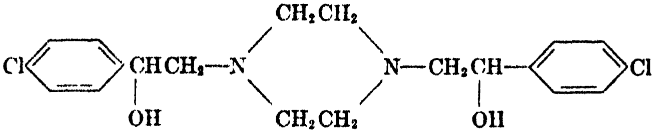
V

SN-12707 Q = <0.3



VI

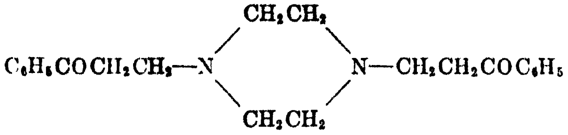
SN-13028 Q = 0.1



VII

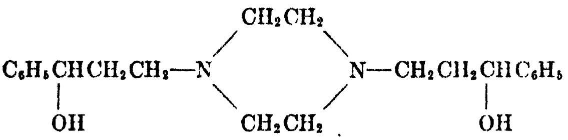
SN-8478 Q = <0.1

Typical homologs of the piperazyl diketones and dialcohols also were made. These included the two diketones, VIII (3) and X, made by the Mannich reaction on acetophenone and *p*-chloroacetophenone. The first of these two (VIII) was reduced successfully without fission to the piperazyl dialcohol (IX).



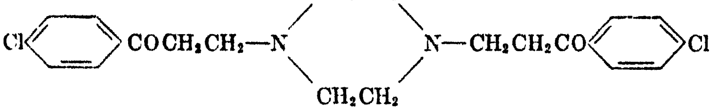
VIII

SN-3689 Q = <0.08



IX

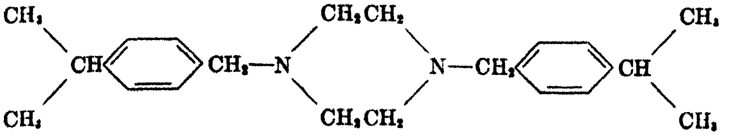
SN-8119 Q = <0.1



X

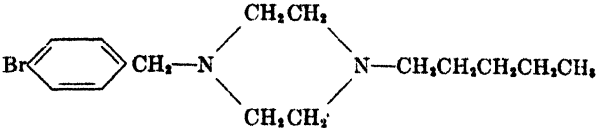
SN-7388 Q = <0.08

The following two new N,N'-dialkylpiperazines were made and tested:



XI

SN-8120 Q = <0.6



XII

SN-9587 Q = <0.15

EXPERIMENTAL[5, 6]

The preparation of 1-benzylpiperazine differed slightly in detail from the directions of Baltzly *et al.* (4). To a solution of 144 g. (1.8 moles) of anhydrous piperazine in 500 ml. of absolute ethanol was added over twelve minutes with stirring, 76 g. (0.6 mole) of benzyl chloride. After standing overnight, and filtering off the precipitate, the ethanol was evaporated under reduced pressure and the residual oil was partitioned between equal volumes of ether and 3 *N* sodium hydroxide. The aqueous layer was extracted twice with ether and the ether solution evaporated. The oil thus obtained was fractionated; yield 47 g. (45%); b.p. 128–135° (6 mm.).

1-(n-Amyl)piperazine. To 431 g (5 moles) of anhydrous piperazine in 1.2 l. of methanol was added 396 g. (2 moles) of amyl iodide over ten minutes, with stirring and cooling to take care of the considerable heat of reaction. After standing for four days and filtering from precipitated salts, the methanol was distilled and the product dissolved in ether and washed three times with 3 *N* sodium hydroxide to remove excess piperazine. Evaporation of the ether gave 343 g. of oil which was fractionated; yield 161 g. (52%) of hygroscopic oil; b.p 105–110° (9 mm.); n_D^{20} 1.4650–1.4659.

The *dihydrochloride* was obtained from ether by addition of ethereal hydrogen chloride; two recrystallizations from isopropanol gave colorless rods of m.p. 267–269°.

Anal. Calc'd for $C_9H_{20}N_2 \cdot 2HCl$: Cl^-, 30.94. Found: Cl^-, 30.90.

1,4-Di-(4-isopropylbenzyl)piperazine (XI). A mixture of 13.2 g. (0.15 mole) of piperazine, 100 ml. of methanol, and 42.2 g. (0.25 mole) of *p*-isopropylbenzyl chloride was heated almost to boiling and allowed to stand at room temperature overnight. The tan precipitate, after cooling in ice, was filtered and washed with water to remove piperazine hydrochloride, and was treated with 2.5 *N* sodium hydroxide and extracted with ether. Evaporation under reduced pressure gave 14.6 g. of solid which was recrystallized from ethanol; 9.3 g. (18% from piperazine); hexagonal rods; m.p. 83–84°. After repeated recrystallizations from ethanol it melted at 84–85.°

Anal. Calc'd for $C_{24}H_{34}N_2$: N, 7.99. Found: N, 8.03.

The *dihydrochloride* was prepared from ether with ethereal hydrogen chloride and was recrystallized from ethanol; rectangular plates; m.p. 274–275° (*in vacuo*).

Anal. Calc'd for $C_{24}H_{34}N_2 \cdot 2HCl$: N, 6 62. Found: N, 6.83

1-(n-Amyl)-4-(4-bromobenzyl)piperazine dihydrochloride (XII). A mixture of equimolar amounts of *p*-bromobenzyl bromide and 1-*n*-amylpiperazine in ether was refluxed for five

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[5] All melting points are "corrected".

[6] Microanalyses were by Miss Geraldine Alley, Mrs. Joyce Blume Caliga, R. J. Rowlett, Jr., J. W. Wilson, III, and C. S. Floyd.

minutes (with formation of a crystalline precipitate). After treatment of the ether solution with aqueous sodium carbonate, separation, washing, and drying over sodium sulfate, the product was precipitated as the dihydrochloride with ethereal hydrogen chloride. Recrystallization from ethanol gave a 56% yield; m.p. 275–277° (*in vacuo*).

Anal. Calc'd for $C_{16}H_{25}BrN_2 \cdot 2HCl$: Cl^-, 17.81. Found: Cl^-, 17.85.

1-n-Amyl-4-(p-chlorophenacyl)piperazine dihydrochloride (I). A suspension of 70 g. (0.3 mole) of *p*-chlorophenacyl bromide in 450 ml. of ether was treated over three minutes with 46.9 g. (0.3 mole) of 1-*n*-amylpiperazine; a precipitate began to form almost immediately; 450 ml. of 1 *N* sodium carbonate was added and the mixture was shaken for 24 hrs The ether layer was separated, dried over sodium sulfate, and treated with ethereal hydrogen chloride. The largely crystallized product was digested with isopropanol, filtered, and washed with ether; 85 g. (79%). A portion of this was reduced (see below). Recrystallization from ethanol gave rhombic prisms of m.p. 235° decomp.

Anal. Calc'd for $C_{17}H_{25}ClN_2O \cdot 2HCl$: N, 7.34. Found: N, 7.61.

α-4-Chlorophenyl-β-(1-n-amyl-4-piperazyl)ethanol dihydrochloride (III). Reduction was carried out in the usual way with aluminum isopropoxide (see VII), under refluxing for eight hours, with hydrolysis in 10 *N* sodium hydroxide and extraction of the product by ether. Since the product did not crystallize upon evaporation of the solvent, it was converted into the hydrochloride by ethereal hydrogen chloride. The yield after two recrystallizations from ethanol (one with Darco treatment) was 31%; white rhombic crystals; m.p. 241–242° (*in vacuo*).

Anal. Calc'd for $C_{17}H_{27}ClN_2O \cdot 2HCl$: N, 7.30. Found: N, 7.43.

1-Benzyl-4-(4-chlorophenacyl)piperazine dihydrochloride (II). To 46.8 g. (0.2 mole) of *p*-chlorophenacyl bromide in 300 ml. of ether was added slowly 35.2 g. (0.2 mole) of 1-benzylpiperazine. When the precipitation had apparently ceased, 42 g. of sodium carbonate in 300 ml. of water was added and the mixture was shaken for 24 hours. The ether layer was separated, dried over sodium sulfate, and acidified (to Congo) with ethereal hydrogen chloride; the product, washed repeatedly with ether (69.7 g.; 87%), melted at 236–240° (sintering). Recrystallization from ethanol gave cubic prisms; sintered at 237–239° *in vacuo*.

Anal. Calc'd for $C_{19}H_{21}ClN_2O \cdot 2HCl$: Cl^-, 17.65. Found: Cl^-, 17.62.

α-4-Chlorophenyl-β-(1-benzyl-4-piperazyl)ethanol (IV) was prepared from the piperazine diketone dihydrochloride (II) in the usual way by aluminum isopropoxide reduction (under reflux for 13 hrs.). The crude product, as the base, was crystallized from ethanol as fluffy crystals (rods) of m.p. 152° in a yield of 59%. Recrystallization from ethanol did not raise the melting point.

Anal. Calc'd for $C_{19}H_{23}ClN_2O$: N, 8.47. Found: N, 8.59.

1,4 Diphenacylpiperazine (V). A suspension of 39.8 g. (0 2 mole) of phenacyl bromide in 170 ml. of 95% ethanol was treated by slow addition of 8.6 g. (0.1 mole) of piperazine under stirring; heat was evolved and a copious precipitate formed. Sodium carbonate (21 g.; 0.2 mole) was added slowly and stirring continued for 30 min. After cooling and filtering, addition of 150 ml. of hot water, and again filtering, the solid was slurried with 200 ml. of hot water, filtered, and washed with three 50-ml. portions of hot water; cubic prisms; 25 g.; m.p. 139–142°. Recrystallization from 300 ml. of 25% ethanol and 100 ml. of ethyl acetate gave 23 g. (71.5%); m.p. 141–142°. The melting point was not raised upon repeated recrystallizations.

Anal. Calc'd for $C_{20}H_{22}N_2O_2$: N, 8.69. Found: N, 8.90.

It was soluble in ethyl acetate, slightly soluble in ethanol and insoluble in ether and water.

1,4-Di-(4-chlorophenacyl)piperazine (VI). Piperazine [8.6 g (0.1 mole)] was added with stirring to a suspension of 46.4 g. (0.2 mole) of *p*-cholorophenacyl bromide in 200 ml. of ethanol. The mixture became warm and the *p*-chlorophenacyl bromide partially dissolved. Sodium carbonate (21 g., 0.2 mole) was added with stirring and the mixture was refluxed for 1.5 hours and allowed to stand at room temperature for twelve hours. A cream-colored solid precipitated during this time. The mixture was thoroughly chilled in an ice-bath and the solid was filtered and washed, once with 50% ethanol and seven times with water; 34.3 g. (88%); m.p. 156–158°. Recrystallization was effected by dissolving the solid in a 4:1 mixture of warm dioxane and ethanol and diluting with 100 ml. of water; colorless rhomboids; 21.4 g. (54%); m.p. 156–158°. It was soluble in dioxane but only slightly soluble in ethanol and insoluble in ether

Anal. Calc'd for $C_{20}H_{20}Cl_2N_2O_2$: N, 7.16. Found: N, 7.21.

1,4-Di-[β-(4-chlorophenyl)-β-hydroxyethyl]piperazine (VII). A mixture of 25.5 g. (0.065 mole) of the piperazine diketone (VI) and 165 ml. of 2.5 *N* aluminum isopropoxide was heated under a fractionating column under partial reflux (4.5 hrs.) until a negative test for acetone was obtained (2,4-dinitrophenylhydrazine). The solvent was distilled under diminished pressure and the product treated with 10 *N* sodium hydroxide and crystallized several times from toluene; m.p. 186–187°. It was difficultly soluble in ethanol, ethyl acetate and dioxane.

Anal. Calc'd for $C_{20}H_{24}Cl_2N_2O_2$: N, 7.09. Found: N, 7.30.

The *preparation of 1,4-bis-(β-benzoylethyl)piperazine dihydrochloride* (VIII) was according to the method of Mannich and Lammering (3); yield 65%; sintered and turned dark at 203°; after one recrystallization from 50% ethanol it melted at 205° (dec.) (M and L., 190° dec.).

1,4-Bis-(γ-hydroxy-γ-phenylpropyl)piperazine (IX). A mixture of 25 g. (0.06 mole) of the above diketone dihydrochloride (VIII), 150 ml. of dry isopropanol and 65 ml. of 3 *N* aluminum isopropoxide was heated under reflux for seven hours, and three hours more after addition of 70 ml. additional 3 *N* aluminum isopropoxide; only toward the end of the reduction period did the test for acetone become negligible. The isopropanol was distilled under reduced pressure. The residue was shaken with 6 *N* sodium hydroxide for half an hour. The brown precipitate was filtered, washed with water, dried, and then washed with ether, which removed the brown color; white solid; 11.7 g. (46%); m.p 154–157°. Upon treatment with 100 ml. of 6 *N* hydrochloric acid, it momentarily dissolved and the dihydrochloride precipitated. This was filtered, reconverted to the base, and crystallized first from butanone and then from ethanol; m p. 158–161°. It was soluble in ethanol, butanone, and dilute hydrochloric acid.

Anal. Calc'd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90.
Found: C, 74.66; H, 8.65; N, 7.89.

1,4-Di-[γ-(4-chlorophenyl)-γ-ketopropyl]piperazine dihydrochloride (X). A mixture of 17.2 g. (0.2 mole) of piperazine, 40 ml. of concentrated hydrochloric acid, 200 ml. of absolute ethanol, 64 g. (0.415 mole) of *p*-chloroacetophenone, and 18 g. (0.6 mole) of paraformaldehyde was refluxed for 3 hrs. and allowed to stand overnight. The white needle crystals were filtered and washed with ether; 75 g. (77%)· m.p. 210° decomp. After recrystallization from water it melted at 212° decomp.

Anal. Calc'd for $C_{22}H_{24}Cl_2N_2O_2 \cdot 2HCl$: Cl^-, 14.41. Found: Cl^-, 14.48.

SUMMARY

New derivatives of piperazine made for screening tests against avian malaria, include two N-alkylpiperazyl alcohols and the corresponding ketones, several N,N′-piperazyl-α-bis-acetophenones and β-bis-propiophenones and the corresponding dialcohols, and two N,N′-dialkylpiperazines.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF
THE UNIVERSITY OF VIRGINIA]

ANTIMALARIALS.[1] SOME NEW LONG-CHAIN ALIPHATIC DI-(AMINO ALCOHOLS)

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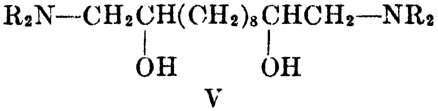
In view of the interest in long-chain diamines, diamidines, diguanidines, and di-(amino alcohols) (1, 2, 3, 4, 5) in connection with the malaria problem, the synthesis of some new compounds in the latter field was undertaken in 1942, but the investigation was soon discontinued in favor of more promising leads. Only a few compounds of the di-(amino alcohol) type had been made up to this time, notably the di-(diethylamino and piperidino alcohols) with twelve-carbon chains (5) and the di-(*tert.*-amino *tert.*-alcohol) made by the addition of methylmagnesium iodide to 1,14-dipiperidyltetradecanedione-2,13 (5).

The series here reported, made from sebacic acid, was chosen for study primarily because of the ready availability of the starting materials. The synthetic procedure was similar to that employed by Work (5). Sebacyl chloride (I) was converted in 87–91% yields through diazomethylation and hydrobromination into the di-(bromomethyl ketone) (III), and this upon condensation with the appropriate secondary amines gave the di-(aminomethyl ketones) (IV) which were reduced catalytically or by aluminum isopropoxide to the di-(amino alcohols) (V). Work (5), who had used the di-(chloromethyl ketone), had found the aluminum isopropoxide method to be impractical under his circumstances.

$$\underset{\text{I}}{ClCO(CH_2)_8COCl} \xrightarrow{CH_2N_2} \underset{\text{II}}{N_2CHCO(CH_2)_8COCHN_2} \xrightarrow{HBr}$$

$$\underset{\text{III}}{BrCH_2CO(CH_2)_8COCH_2Br} \xrightarrow{NHR_2}$$

$$\underset{\text{IV}}{R_2N{-}CH_2CO(CH_2)_8COCH_2{-}NR_2} \xrightarrow{Pt + H_2}$$



$$R_2N{-}CH_2\underset{\displaystyle OH}{\underset{|}{C}}H(CH_2)_8\underset{\displaystyle OH}{\underset{|}{C}}HCH_2{-}NR_2$$

V

The compounds prepared for screening tests are listed in the Table.

The condensations of the amines with the di-(bromomethyl ketone) proceeded rapidly but the yields of the di-(amino ketones) were small (25–40%); the compounds were often oils and except in the case of the tetrahydroisoquinolyl compound, tended to be unstable and to undergo decomposition on long standing; the hydrochlorides were stable.

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[1] A portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

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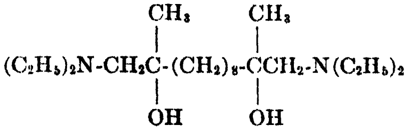
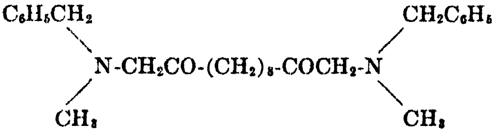
The catalytic reductions of the di-(amino ketones) were slow and it was found to be important to use pure materials. In this connection it should be noted that Work (5) in his platinum catalyzed reduction of two unpurified di-(amino ketones), the di(diethylamino) and dipiperidyl compounds, found the reactions to be slow and incomplete.

The aluminum isopropoxide reduction method was used in several cases where the di-(amino ketones) were not pure enough to warrant a catalytic reduction.

TABLE 1

DI-(AMINO ALCOHOLS)

	SN[3]	
VI	4672	$(C_2H_5)_2N\text{-}CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2\text{-}N(C_2H_5)_2$
VII	4908	 $(C_2H_5)_2N\text{-}CH_2\overset{CH_3}{\underset{OH}{C}}\text{-}(CH_2)_8\text{-}\overset{CH_3}{\underset{OH}{C}}CH_2\text{-}N(C_2H_5)_2$
VIII	4901	$(Butyl)_2N\text{-}CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2\text{-}N(butyl)_2$
IX	6421	
X	—	Morpholinyl-$CH_2CO\text{-}(CH_2)_8\text{-}COCH_2$-morpholinyl
XI	3933	Piperidyl-$CH_2CO\text{-}(CH_2)_8\text{-}COCH_2$-piperidyl
XII	3934	Piperidyl-$CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2$-piperidyl
XIII	3643	Tetrahydroisoquinolyl-$CH_2CO\text{-}(CH_2)_8\text{-}COCH_2$-tetrahydroisoquinolyl
XIVA	5033	Tetrahydroisoquinolyl-$CH_2\text{-}CHOH\text{-}(CH_2)_8\text{-}CHOH\text{-}CH_2$- tetrahydroisoquinolyl
XIVB	6346	The stereoisomer of XIVA

Here the reductions also proceeded slowly as compared with the usually much more rapid reductions of the ordinary aryl amino ketones (6).

The di-tetrahydroisoquinolyl compounds were of special interest because one of them (XIVB) showed slight but definite antimalarial activity against avian malaria. In the case of the di-(amino alcohol) one isomer (XIVA, of m.p. 120–121°) was isolated in a pure condition; however the other sample (XIVB of m.p. 102–103°; Q[4] = 0.1), while it is believed to be the nearly pure stereoisomer, might be a constant crystallizing mixture since it gives no mixture melting point depression with XIVA.

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[3] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned are tabulated in the monograph (7).

[4] This is the A-1 screening test against *gallinaceum* in the chick, determined under the direction of Dr. G. Robert Coatney of the National Institute of Health.

ACKNOWLEDGMENTS

The preparation of XII (Work, ref. 5) was carried out by Mr. Robert J. Keller, III. Microanalyses were by Dr. R. J. Rowlett, Jr. and Misses C. H. Vondra, Geraldine Alley, and Mrs. Joyce Blume Caliga.

EXPERIMENTAL[5]

1,12-Dibromododecanedione-2,11 (III). A solution of 58 g. (0.243 mole) of sebacyl chloride in 75 ml. of absolute ether was added slowly under stirring to 60 g. (1.43 moles) of diazomethane in 2 l. of ether (5–10°) over three hours; the di-(diazomethyl ketone) (II) separated as a solid but was not isolated; a small sample melted at 84–86° [W. (5), 91°]. After standing overnight at room temperature 235 g. (1.22 mole) of 42% hydrobromic acid in 200 ml. of ether was added slowly under stirring (18°); the di-(bromomethyl ketone) appeared in the form of a light yellow solid. After standing 8–10 hours (the evolution of nitrogen had ceased) the mixture was cooled to 0° and the product was filtered; 75 g. (87%); m p. 97–98°. After repeated crystallizations from ethanol it melted at 102–103°.

Anal. Calc'd for $C_{12}H_{20}Br_2O_2$: C, 40.47; H, 5.66.

Found: C, 40.62; H, 5.97.

1,12-Di-(diethylamino)dodecanediol-2,11 (VI). A suspension of 40 g. (0.112 mole) of the di-(bromomethyl ketone) in a mixture of 41 g. (0.56 mole) of diethylamine and 400 ml. of absolute ether was warmed to 30° to initiate reaction, and after standing for one hour the diethylamine hydrobromide was filtered (32 g.; 93%). Evaporation of the solvent and excess diethylamine under reduced pressure left a red oil which failed to yield a crystalline hydrochloride. Extraction with acid, liberation by potassium hydroxide, and isolation by extraction with ether, gave 25 g. (66%) of the base. This was dissolved in 300 ml. of 2.5 *N* aluminum isopropoxide. Reduction was complete after sixty-five hours of refluxing as indicated by a negative acetone test in the distillate. Upon evaporation of the solvent, treatment with 10 *N* potassium hydroxide, and extraction by ether, an oil was obtained which failed to give a crystalline hydrochloride. Fractionation at 2 mm. pressure gave a cut of 10 g. (26%) of b.p. 198–199°; n_D^{25} 1.4618; it also failed to give a crystalline dihydrochloride.

Anal. Calc'd for $C_{20}H_{44}N_2O_2$: N, 8.13. Found: N, 8.38.

The *dipicrate*, obtained by treatment with picric acid in ethanol (warmed to 50°) was recrystallized from ethanol; m.p. 118–121° [W. (5), 121°].

Anal. Calc'd for $C_{32}H_{50}N_8O_{16}$: N, 13.96. Found: N, 14.02

1,12-Diethylamino-2,11-dimethyldodecanediol-2,11 (VII). To a solution of 125 ml. of 1.7 *N* ethereal methylmagnesium iodide was added dropwise at 18° with stirring a 275 ml. absolute ether solution of 30 g. of the crude di-(diethylamino ketone). The reaction was vigorous. After two hours at room temperature and 1.5 hours of refluxing, hydrolysis in ice and dilute hydrochloric acid, and basification with ammonium hydroxide, the product was isolated by evaporation of the ether solution and was fractionally distilled; the cut of b.p. 215–218° (2 mm.) was 9 g. (28%); n_D^{25} 1.4631.

Anal. Calc'd for $C_{22}H_{48}N_2O_2$: N, 7.52. Found: N, 7.85.

1,12-Di-(di-n-butylamino)dodecanediol-2,11 (VIII). A mixture of 20 g. of the di-(bromomethyl ketone), 32 g. of dibutylamine, and dry ether was refluxed for two hours and the resulting secondary amine hydrobromide was filtered. The ether solution was washed with 10% sodium carbonate and dried over sodium sulfate. Evaporation gave 20 g. of oil which was reduced by 150 ml. of 3 *N* aluminum isopropoxide (refluxing until the evolution of acetone ceased). Evaporation of the isopropanol and hydrolysis with potassium hydroxide gave an oil which was fractionally distilled, giving a cut of 12 g. (60%) of b.p. 235–240° (1 mm.); n_D^{20} 1.4657.

Anal. Calc'd for $C_{28}H_{60}N_2O_2$: C, 73.62; H, 13.24.

Found: C, 73.32; H, 13.56.

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[5] All melting points are corrected.

The *dipicrate* formed from ethanol; sinters at 129°.

Anal. Calc'd for $C_{28}H_{60}N_2O_2 \cdot 2C_6H_3N_3O_7$: N, 12.25. Found: N, 12.38.

1,12-Di-(benzylmethylamino)dodecanedione-2.11 dihydrochloride (IX). A suspension of 50 g. (0.14 mole) of the di-(bromomethyl ketone) in 300 ml. of absolute ether was treated with 86 g. (0.71 mole) of benzylmethylamine; the reaction was initiated by warming to 30°, and after one hour the benzylmethylamine hydrobromide was filtered (54 g., 95%). The remaining basic constituents were extracted by 1 *N* hydrochloric acid and liberated; the excess benzylmethylamine was evaporated at 95° (4 mm.) and the residual oil was converted to a crystalline hydrochloride from acetone with ethereal hydrogen chloride; it was recrystallized from an isopropanol-ethyl acetate mixture, with added ethereal hydrogen chloride; three crystallizations from isopropanol (including one Darco treatment) gave 15.5 g. (35%); m p. 157–158°.

Anal. Calc'd for $C_{28}H_{40}N_2O_2 \cdot 2HCl$: C, 65.99; H, 8.31; N, 5.50.
Found: C, 65.78; H, 7.98; N, 5.46.

1,12-Di-(N-morpholinyl)dodecanedione-2,11 (X) was made like XI. The base crystallized upon concentrating the ether solution of the crude product (m.p. 62–63°). It was converted into the dihydrochloride from ethanol by addition of ethereal hydrogen chloride; three crystallizations from isopropanol gave 11 g. (25%) of m.p. 189–190°.

Anal. Calc'd for $C_{20}H_{36}N_2O_4 \cdot 2HCl$; N, 6.35. Found: N, 6.15.

The *base* crystallized from ethanol as blade-shaped scales; m.p. 72 73°.

Anal. Calc'd for $C_{20}H_{36}N_2O_4$: C, 65 18; H, 9.85.
Found: C, 65.05; H, 9.83.

1,12-Di(N-piperidyl)dodecanedione-2,11 (XI). Thirty grams of piperidine was added slowly with stirring to 25 g. of the di-(bromomethyl ketone) suspended in 350 ml. of absolute ether The reaction proceeded slowly, and after one hour and cooling to 0°, the precipitated piperidine hydrobromide was filtered (96%). After repeated washing with water and evaporation of the solvent under reduced pressure, a residue of m.p. 39–40° was obtained. In a separate experiment the product at this point was recrystallized from ethanol and handled as the free base (yield 54%). The melting point reported by Work (5) was 43°. The crude base was converted into the hydrochloride in acetone by ethereal hydrogen chloride. Three crystallizations from isopropanol by addition of ether gave 11.5 g. of pure product (37.5%); m.p. 177–178°

Anal. Calc'd for $C_{22}H_{40}N_2O_2 \cdot 2HCl$: N, 6 40. Found: N, 6.26.

The *dipicrate* formed from ethanol from which it was recrystallized six times, m.p. 127–128°.

Anal. Calc'd for $C_{22}H_{40}N_2O_2 \cdot 2C_6H_3N_3O_7$: C, 49.63; H, 5.63; N, 13.62.
Found: C, 49.72; H, 5.84; N, 13.34

The *dihydrobromide* was recrystallized five times from isopropanol; m.p. 189–190°.

Anal. Calc'd for $C_{22}H_{40}N_2O_2 \cdot 2HBr$: N, 5.32. Found: N, 5 37

The *base* crystallized from dilute ethanol as thin rhombic plates; m.p. 39 5–40°.

Anal. Calc'd for $C_{22}H_{40}N_2O_2$: C, 72 47; H, 11.06; N, 7.69
Found: C, 72.24; H, 11.11, N, 7 40.

1,12-Di-(N-piperidyl)dodecane-2,11-diol (XII) (5) Reduction of 10 g of the free di-(amino ketone) (m.p. 36–38°) in ethanol using platinum oxide proceeded slowly and stopped with absorption of one mole. Evaporation of the solvent under reduced pressure gave an oil which solidified on cooling in ice It was recrystallized from acetone (m p. *ca.* 60°) and converted into the hydrochloride from acetone with alcoholic hydrogen chloride and addition of ether; yield 3.3 g. (27.5%); m p 234–236°; recrystallized from isopropanol; m.p. 246.5–247.5°.

Anal. Calc'd for $C_{22}H_{44}N_2O_2 \cdot 2HCl$: N, 6.48. Found: N, 6.50

The base was first recrystallized from an ethanol-water mixture (flat rhombohedral plates); repeated recrystallizations from dilute ethanol or acetone brought the melting point to 80–80.5° [W. 78° (5)].

Anal. Calc'd for $C_{22}H_{44}N_2O_2$: C, 71.68; H, 7.81.
Found: C, 71.89; H, 11.84.

The *dipicrate* melted at 151–152° (W. 152°).

Anal. Calc'd for $C_{34}H_{56}N_8O_{16}$: C, 49.39; H. 6.10; N, 13.55.
Found: C, 49.58; H, 6.55; N, 13.28.

1,12-Di(N-1,2,3,4-tetrahydroisoquinolyl)dodecanedione-2,11 (XIII). Forty-five grams (0.388 mole) of tetrahydroisoquinoline was added under stirring and external cooling to 25 g. (0.7 mole) of the di-(bromomethyl ketone) in 300 ml. of absolute ether (two hours); the tetrahydroisoquinoline hydrobromide was filtered off [30 g. (100%)]. Concentration of the ether solution gave 16 g. of crystals (m.p. 68–72°). Two recrystallizations from methanol and one from ligroin-ethyl acetate mixture gave 12 g. (37%) of m.p. 77–78°. It crystallized also from isopropanol-water mixtures.

Anal. Calc'd for $C_{30}H_{40}N_2O_2$: N, 6.08. Found: N, 6.39.

1,12-Di-(N-1,2,3,4-tetrahydroisoquinolyl)dodecanediol-2,11-A and -B (XIV A and B). Reduction of 8.83 g. of XIII (partially dissolved) in 300 ml. of methanol using 0.876 g. of platinum oxide at 26° and atmospheric pressure proceeded very slowly; one equivalent of hydrogen was absorbed over sixty-three hours (from time to time additional catalyst was added), and the reaction came to a stop. Upon filtering and cooling to 0°, 6.5 g. of crystals (m.p. 105–112°) separated. One crystallization from methanol, two from ligroin-ethyl acetate mixture, and a fourth from isopropanol brought the melting point to 120–121°. This product is designated as XIV A.

Anal. Calc'd for $C_{30}H_{44}N_2O_2$: C, 77.53; H, 9.55; N, 6.03.
Found: C, 77.32; H, 9.27; N, 5.75.

Four grams of material recovered from the solvents used in the above crystallizations was recrystallized once from methanol, twice from isopropanol, and twice from ligroin-ethyl acetate mixture; the product on the last few crystallizations melted at 102–103°. The sample (1.5 g.) was treated with refluxing isopropanol-aluminum isopropoxide solution (four hours) and recovered with the same melting point (102–103°).

Anal. Calc'd for $C_{30}H_{44}N_2O_2$: C, 77.53; H, 9.55; N, 6.03.
Found: C, 77.48; H, 9.79; N, 6.25.

Reduction in ethyl acetate required seven days, but did not go at all in 1 *N* hydrochloric acid.

SUMMARY

Eight dodecane di-(*tert.*-amino alcohols) were made for antimalarial tests. The syntheses started from sebacyl chloride and involved diazomethylation, hydrobromination of the di-(diazomethyl ketone) and condensation of the resulting di-(bromomethyl ketone) with the following secondary amines: diethylamine, dibutylamine, benzylmethylamine, morpholine, piperidine and tetrahydroisoquinoline. Four of the di-(*tert.*-amino ketones) were isolated; these, and also two which were not isolated, were reduced to the di-(*tert.*-amino alcohols) catalytically or by aluminum isopropoxide. Diastereoisomers were isolated in one case. One di-(*tert.*-amino *tert.*-alcohol) was made by addition of methylmagnesium iodide to a di-(*tert.*-amino ketone).

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[Contribution from the Wm. Albert Noyes Laboratories, University of Illinois]

THE IMPROVED SYNTHESIS OF 5-NITRO-1,10-PHENANTHROLINE

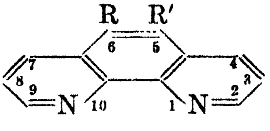
G. FREDERICK SMITH and F. Wm. CAGLE, Jr.

Received January 30, 1947

The application of the ferrous complex of 5-nitro-1,10-phenanthroline as a high potential oxidation-reduction indicator (oxidation potential 1.25 volts) to newly developed procedures in cerate oxidimetry (1, 2), has increased the demand for this indicator. Since the starting material used in its preparation, 1,10-phenanthroline, is itself a somewhat expensive preparation (3), it has heretofore been a distinct disadvantage that the yield of 5-nitro-1,10-phenanthroline prepared from it by the best known method (4) has been relatively low, (60%).

A report is now being given of the successfully attempted development of a new procedure for the preparation of the dye base for preparation of the indicator nitro-ferroin[1] in yields of 90% or better. A study has also been made of the simultaneous formation, in small yield, of a new compound identified as 1,10-phenanthroline-5,6-quinone.

The preparation of most other 1,10-phenanthrolines substituted in the 5 or 5,6 positions of structural formula I where R and R′ are CH_3 and NO_2 respectively or when R is hydrogen and R′ is either CH_3, NO_2, Cl, or Br, follows procedures involving (5) a Skraup synthesis employing the properly substituted 8-aminoquinoline (6, 7). The preparation of 1,10-phenanthroline for the present work involved two successive Skraup reactions starting with ortho-nitroaniline with intermediate reduction of 8-nitroquinoline to the amino derivative (3).



I

The 5-nitro-1,10-phenanthroline may, however, as an exception to the usual case, be prepared by direct nitration of 1,10-phenanthroline or its monohydrate This nitration as originally described (4) results in the formation of the mononitro derivative in a yield of 60% based upon the 1,10-phenanthroline used. Further investigation into the possible formation of a 5,6-dinitro derivative by this reaction was unsuccessful (8).

In distinction from the previously described nitration of 1,10-phenanthroline (4), the influence of two modifications of the usual procedure was predicted to be possibly beneficial. The use of 95% sulfuric acid was altered by substituting 15–25% oleum, and the temperature of the reaction was increased from 120° to 170°. Nitration under these conditions using concentrated nitric acid (sp. gr. 1.42) could be reasonably expected both to increase the yield of finished product and decrease the required reaction time. The well established resistance of the phenanthrolines to destructive decomposition by strong acids in contact with strong oxidants justified the innovations applied.

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[1] Nitro-ferroin is the trivial name for the ferrous complex of 5-nitro-1,10-phenanthroline. This compound is red. The corresponding ferric compound, nitro-ferriin, is faintly blue.

THE NITRATION OF 1,10-PHENANTHROLINE

The directions for the improved nitration of 1,10-phenanthroline, applying the newly developed procedure, are as follows:

Dissolve 30 g. of 1,10-phenanthroline monohydrate in 150 ml. of oleum (25% sulfur trioxide). Add 80 ml. of conc'd HNO_3 (sp. gr. 1.42) with stirring and at such a rate that the temperature approaches but does not exceed 170°. After the addition of nitric acid continue stirring during a 30-min. period.

Carefully pour the reaction mixture thus prepared over 2000 g. of crushed ice. Treat the strongly acid solution, after the ice has melted, with sufficient 30% sodium hydroxide solution to give a reaction mixture neutral to litmus. Add just sufficient dilute nitric acid to reverse the color of the indicator, litmus paper, and filter the insoluble 5-nitro-1,10-phenanthroline, using a 6-inch Büchner funnel, and moderately reduced pressure. Wash the product with cold water to remove soluble products of the reaction.

TABLE I

THE NITRATION OF 1,10-PHENANTHROLINE AND ITS CONVERSION TO 5-NITRO-1,10-PHENANTHROLINE

1,10-PHENANTHROLINE MONOHYDRATE, G	TEMPERATURE OF NITRATION, °C	YIELD, %
3	173	69.4
3	168	72.2
6	168	78.7
30	168	75.2
30	161	81.0
30	165	87.4
30	165	90.1

The 5-nitro-1,10-phenanthroline is a light yellow crystalline compound (m.p. 197–198°). It may be air-dried either at ordinary temperatures or at 60°, or, preferably, in a spacious desiccator over an ample supply of anhydrone to accelerate the removal of adsorbed water.

Data obtained for a series of applications of the described procedure are given in Table I.

By examination of the data of Table I it is seen that the optimum conditions involve heating to 165° during nitration. Best yields are obtained employing moderate amounts of 1,10-phenanthroline. Even better yields (approximately 95%) are attained in nitration of 300-g. portions of starting material.

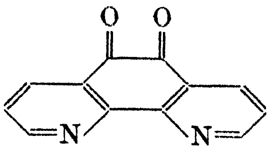
INVESTIGATION OF SECONDARY OXIDATION PRODUCTS OF NITRATION REACTION

The filtrate from the nitration of 30 g. of 1,10-phenanthroline monohydrate was orange-red in color and upon storage during 15 days (with slight evaporation) deposited a small amount of an orange-colored crystalline material. This was found to melt with decomposition at 248–253°. It was recrystallized twice from 95% ethanol, giving 0.7 g. of small, yellow, plate-like crystals having the melting point 256–257°.

Anal. Calc'd for $C_{12}H_6N_2O_2$: C, 68.6; H, 2.88; N, 13.3.

Found. C, 68 3; H, 2.72; N, 13.3.

From the nature of its synthesis and as a result of analysis, the compound $C_{12}H_6N_2O_2$ was postulated to have the structural formula.



It seems unlikely that the keto oxygen would be found on the extremely inert heterocyclic rings. The material was found to be insoluble in water and to form no hydrate under the described conditions of preparation. It gave no colored complex compound with the ferrous ion, in contrast to the parent substance.

Further substantiation for the structural formula assumed was found by confirmatory test reactions. The compound reacts with 2,4-dinitrophenylhydrazine to give in rather poor yield a red hydrazone of m.p. above 300°. This material can be recrystallized from pyridine, in which it is slightly soluble at the boiling point, and almost insoluble at room temperature. The 2,4-dinitrophenylhydrazone is almost insoluble in boiling ethyl acetate and only very slightly soluble in boiling benzene. A sample recrystallized twice from pyridine was used for microanalysis and found to be the mono substituted derivative.

Anal. Calc'd for $C_{18}N_{10}N_6O_5$: C, 55.39; H, 2.58; N, 21.53
Found: C, 55.29; H, 2.62; N, 20.81.

The agreement of the nitrogen in the analysis leaves something to be desired, but considering the nature of the material and difficulty of purification by crystallization, it was felt that the results were satisfactory.

The compound also reacts with ethylenediamine exothermally to give a product of very high m.p. and wide fusion range. The substance gives the test described by Feigl (9) for a 1,2-diketone. An additional amount of (about 0.5 g.) of this 1,10-phenanthroline-5,6-quinone can be obtained by evaporation of the filtrate from the first batch recovery until sodium sulfate begins to separate.

Attempts to prepare this compound by oxidation of 1,10-phenanthroline employing acidified dichromate, neutral, acid, or alkaline peroxide, acidified vanadate or periodate, all failed. This is in agreement with a recent report (10) of the attempted oxidation of 1,7- and 4,7-phenanthrolines to form ortho-quinones.

The fact that this compound does not form a colored complex with ferrous iron (the ferroin reaction) may be due to the lack of possible resonance in the benzene nucleus of the molecule.

ACKNOWLEDGMENT

The microanalyses reported in this paper were made by H. S. Clark of The Illinois State Geological Survey. The 1,10-phenanthroline used in this investigation was donated by The G. Frederick Smith Chemical Company of Columbus, Ohio. Thanks is proferred for this assistance.

RÉSUMÉ

Directions have been given for the improved synthesis of 5-nitro-1,10-phenanthroline by direct nitration of 1,10-phenanthroline. Former optimum yields (following previously described directions for nitration) of 60% have been improved to 90% yield of finished product.

The isolation of a by-product, 1,10-phenanthroline-5,6-quinone, in small yield has been described.

URBANA, ILL.

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

THE REACTION PRODUCT OF AZOXYBENZENE AND CHLOROSULFONIC ACID[1]

IRWIN A. PEARL AND ANTHONY R. RONZIO[2]

Received April 17, 1947

The preparation of azobenzene, azoxybenzene, and sodium *p*-azobenzenesulfonate by the reduction of nitrobenzene with sulfite waste liquor was described in recent papers (1, 2). Both azobenzene and sodium *p*-azobenzenesulfonate, upon treatment with chlorosulfonic acid, yielded *p*-azobenzenesulfonyl chloride which in turn was successfully used for the preparation of sulfanilamide derivatives (3). This latter study prompted the investigation of the chlorosulfonation of azoxybenzene (the chief product of the reduction of nitrobenzene by sulfite waste liquor at atmospheric pressure) and the possible use of azoxybenzenesulfonyl chloride for the preparation of sulfanilamide derivatives.

Azoxybenzene (I) reacted smoothly with chlorosulfonic acid at room temperature, at 100°, or in a solvent to yield a compound (II) as translucent orange platelets, insoluble in cold sodium hydroxide, melting sharply at 117–118° and corresponding to the empirical formula for azoxybenzenesulfonyl chloride (III), $C_{12}H_9ClN_2O_3S$. Reaction of (II) with aqueous ammonia did not give the desired azoxybenzenesulfonamide, but yielded only *p*-hydroxyazobenzene (IV). Further attempts to prepare azoxybenzenesulfonamides were equally fruitless.

The failure of (II) to condense with ammonia or other amines, indicating that (II) might not have the structure (III), prompted a more comprehensive study of the compound in order to account for its anomalous behavior.

The experiments described in this paper have enabled us to assign to compound (II) the structure—*p*-azobenzene chlorosulfonate[3].

A saturated alcoholic solution of (II) gave no precipitate with either alcoholic silver nitrate or alcoholic barium chloride. Refluxing with absolute ethanol in the presence of concentrated sulfuric acid yielded only the original (II). No reaction was obtained by warming with concentrated sulfuric acid at 60°. Boiling of (II) with sodium hydroxide solution gave (IV), sodium sulfate, and sodium chloride as the chief reaction products, together with small amounts of azobenzene and *p*-chloroazobenzene. Boiling (II) with concentrated ammonium hydroxide yielded the theoretical amount of (IV) but no azobenzene or *p*-chloroazobenzene.

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[1] This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

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[3] Note added October 17, 1947. While this article was in press, *Chemical Abstracts* **41**, 5472 (Sept. 10, 1947) was received; this contains an abstract of an article by Lukashevich and Sokolova (*Compt. rend. acad. sci U R S S.* **54**, 693 (1946)), in which the authors describe *p*-azobenzene chlorosulfonate (which they designate as *p*-hydroxyazobenzene chlorosulfonate). They prepared the compound in 70% yield by treating azoxybenzene in a little carbon tetrachloride with a ten-fold excess of chlorosulfonic acid at a temperature below −8°. The melting point of their compound is identical with that of the compound described in this paper.

Reduction of (II) with stannous chloride in alcoholic hydrochloric acid solution or with zinc in aqueous hydrochloric acid solution yielded hydrogen sulfide, *p*-aminophenol, and aniline. Reduction with zinc in sulfuric acid solution yielded chloride ions. Hydrogenation of (II) over Raney nickel in benzene at 50 lbs. yielded aniline, *p*-aminophenol, hydrogen sulfide, and hydrogen chloride.

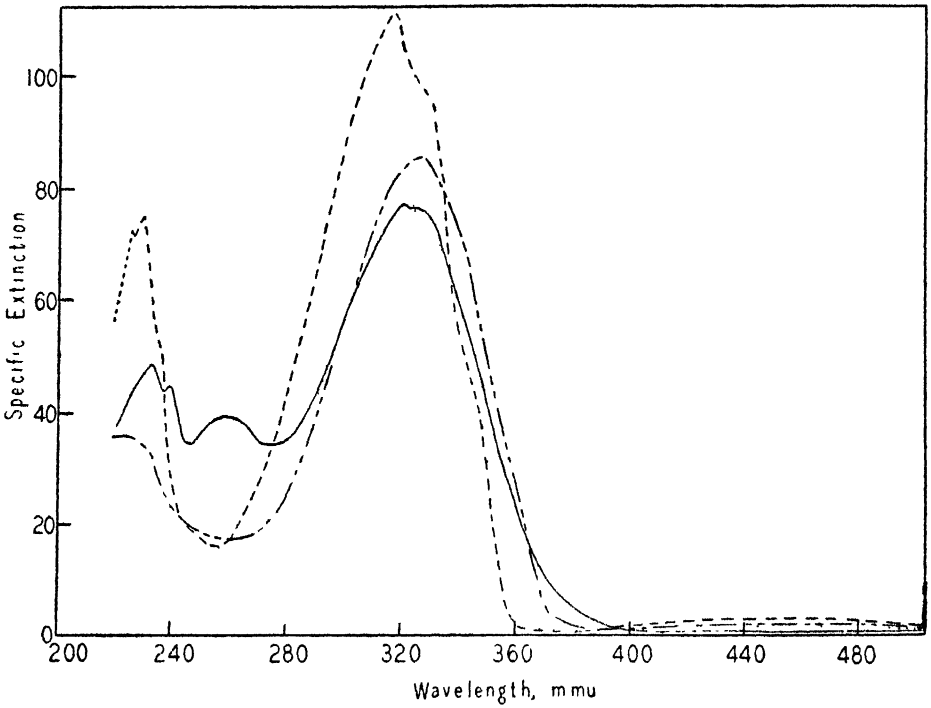


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA FOR COMPOUNDS IN *n*-HEPTANE

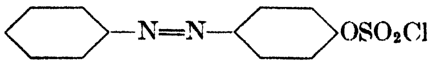
- - - - - - - - Azobenzene
———————— Azoxybenzene
—-—-—-—- *p*-Azobenzenesulfonyl chloride
. . . . *p*-Azobenzene chlorosulfonate (Compound II)

The molecular weight of (II) was determined by the freezing point method in three different solvents. In benzene the molecular weight was found to be 295. However, in camphor and dioxane values of 149 and 557 were obtained, indicating dissociation and association, respectively, in these two solvents.

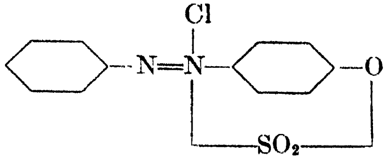
Ultraviolet absorption spectra were obtained and compared with those of azobenzene, azoxybenzene, and *p*-azobenzenesulfonyl chloride. These curves are shown in Figure 1.

DISCUSSION

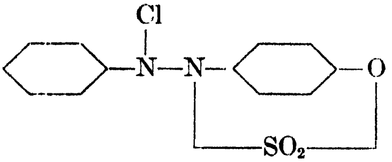
Of the many possible structures for compound (II) those possessing a sulfur atom para to the two nitrogen atoms are precluded by the hydrogenation and reduction experiments in which *p*-aminophenol is obtained as one of the reduction products. The many experiments in which (IV) is formed as a result of the alkaline treatment of (II) further support this conclusion. Thus, the following formulas remain as possibilities:



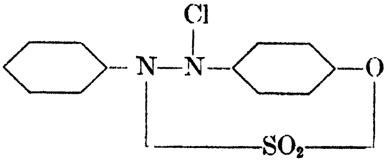
(IIa)



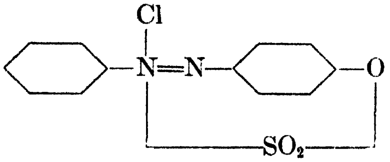
(IIb)



(IIc)



(IId)



(IIe)

Although the chemical data do not provide us with the required evidence to eliminate any of these structures, the ultraviolet absorption data and color of the compound enable us to choose (IIa) on the basis of the similarity of the spectra of compound (II), azobenzene, and *p*-azobenzenesulfonyl chloride. Only this structure possesses the unsubstituted chromophoric azo group.

The ultraviolet absorption spectrum of azobenzene in *n*-heptane determined with a Beckman spectrophotometer at minimum slit width is shown in Figure 1. The curve thus obtained indicates more detail than curves reported in the literature. The ultraviolet absorption of azobenzene has been studied by many investigators. On the basis of all work prior to 1929, Henri (4) has reported maxima at 230 mmu, 310 mmu, and 435 mmu, and minima at 210 mmu, 255 mmu, and 380 mmu for the absorption spectrum of azobenzene in hexane. Brode (5), working with an alcoholic solution, noted a break at 345 mmu. In addition we have found a maximum at 225 mmu, a minimum at 227 mmu, and breaks in the curve at about 237 mmu and about 325 mmu.

Similarly, the curve obtained for azoxybenzene under the same conditions contains more detail than those in the literature. Ramart-Lucas and Biquard (6) reported maxima at 260 mmu and 320 mmu and minima at 245 mmu and

275 mmu for azoxybenzene in hexane. Szegö (7) noted another maximum at 230 mmu and breaks in the curve at 300 mmu and 375 mmu. Our curve shows an additional maximum at 239 mmu, a minimum at 237 mmu, breaks in the curve at 228 mmu and 322 mmu, and a very weak and diffuse fundamental band at 430 mmu.

The curve for compound (II) contains all the essential characteristics of the azobenzene curve, in fact much more so than that of *p*-azobenzenesulfonyl chloride prepared from azobenzene and chlorosulfonic acid. The maxima at 230 mmu, 320 mmu, and 440 mmu and minima at 255 mmu and 380 mmu, and even the breaks in the curve at 325 and 345 mmu are retained. On the basis of this similarity with the azobenzene curve and the dissimilarity with the azoxybenzene curve, it appears that compound (II) contains the azobenzene nucleus.

In order to determine whether this anomalous reaction took place by way of the Wallach rearrangement of azoxybenzene to *p*-hydroxyazobenzene, the latter compound was treated with chlorosulfonic acid under a variety of conditions, but no *p*-azobenzene chlorosulfonate could be isolated. Attempts to prepare *p*-azobenzene chlorosulfonate by the reaction of sulfuryl chloride and *p*-hydroxyazobenzene were equally unsuccessful. Therefore, it appears that rearrangement and chlorosulfonation take place simultaneously or chlorosulfonation must take place on the oxygen of the azoxy group before rearrangement occurs.

Acknowledgment. The authors are indebted to the Analytical Department of The Institute of Paper Chemistry under the direction of Dr. B. L. Browning for the microanalyses and ultraviolet spectral data reported in this paper.

EXPERIMENTAL

All melting points given are uncorrected.

The preparation of compound (II) (p-azobenzene chlorosulfonate). A. Room temperature. In a 2-liter flask surrounded by a cooling bath was placed 580 g. of chlorosulfonic acid. With vigorous stirring 198 g. of azoxybenzene was gradually added over a period of 30 minutes, with the temperature maintained at 30°. After all the azoxybenzene had been added, the black mixture was stirred for 2 hours at room temperature, and then poured with stirring into 3 liters of crushed ice and water. The mixture was allowed to stand overnight. The light brown, powdery precipitate was filtered, washed with water, and dried as thoroughly as possible by suction. The semidry precipitate was then vigorously agitated with an ice-cold dilute sodium hydroxide solution to remove any *p*-hydroxyazo material. Very little dissolved. After 2 hours, the precipitate was filtered, washed with water, and then dried in a vacuum desiccator. The yield was 275 g. The crude product was dissolved in boiling ether, filtered, concentrated to incipient crystallization, and cooled. The orange crystals which separated were filtered and recrystallized from petroleum ether (65–110°) to give translucent orange platelets melting at 117–118°.

Anal. Calc'd for $C_{12}H_9ClNO_3S$: C, 48.69, H, 3.03; Cl, 11.96; N, 9.45; S, 10.81.
Found: C, 48.82; H, 3.19; Cl, 11.91; N, 9.88; S, 10.74.

B. High temperature. Into a 1-liter 3-neck flask, equipped with a mechanical stirrer and a thermometer reaching below the level of the reaction mixture, was placed 290 g. of chlorosulfonic acid. With vigorous stirring 100 g. of azoxybenzene was added gradually over a period of 30 minutes A violent reaction, with the evolution of yellow fumes, took place. No external cooling was applied and the temperature rose to 110°. Stirring was continued for one hour and then the mixture was heated on the steam-bath with stirring for an additional hour to complete the reaction. After cooling, the mixture was slowly poured into 2 liters of crushed ice and water with vigorous stirring. The granular golden precipitate which separated was purified as above to yield orange platelets melting at 117–118° and not depressing the melting point in mixture with the compound prepared at room temperature.

C. In a solvent. To a solution of 18.8 g. of azoxybenzene in 250 ml. of carbon tetrachloride was added dropwise with vigorous stirring, 11.6 g. of chlorosulfonic acid. After approximately one-half of the acid was added, reaction set in and an oily precipitate separated. After all the acid was added, stirring was continued for a short while and the solvent was then decanted from the precipitate. The solvent layer was washed with water, dried with anhydrous sodium sulfate, and evaporated to give 8.9 g. of azoxybenzene. The oily precipitate was treated with water which caused it to solidify. After filtering, washing with water, and drying in a vacuum desiccator, it was recrystallized from methanol and petroleum ether to give 14.6 g. of orange platelets melting at 117–118° and not depressing the melting point in mixture with the compound prepared at room temperature.

Reaction of compound (II) with ammonia. A. A mixture of 5 g. of compound (II) and 50 cc. of concentrated ammonium hydroxide was allowed to stand for 24 hours at room temperature. The clear solution which resulted was acidified with dilute hydrochloric acid, giving an orange precipitate. This was filtered, washed, air dried, and recrystallized from benzene to give 3 g. of *p*-hydroxyazobenzene melting at 150–151°. A mixed melting point with authentic *p*-hydroxyazobenzene prepared from azoxybenzene and sulfuric acid (8) was not depressed.

Anal. Calc'd for $C_{12}H_{10}N_2O$: C, 72.8; H, 5.05; N, 14.14.
Found: C, 73.0; H, 5.13; N, 14.31.

B. A solution of 5 g. of compound (II) in 250 cc. of ordinary U.S.P. ether was saturated with gaseous ammonia below 20°. The precipitate which formed was filtered and recrystallized from ethanol and decolorizing carbon. Colorless platelets of ammonium sulfamate melting at 130–131° were obtained. A mixed melting point with authentic ammonium sulfamate was not depressed.

Anal. Calc'd for $H_6N_2O_3S$: N, 24.56; S, 28.07.
Found: N, 24.59; S, 28.81.

The ether was evaporated and the residue was taken up in water and acidified with dilute hydrochloric acid. Recrystallization of the precipitate from benzene yielded *p*-hydroxyazobenzene.

Similar experiments in both warm and cool anhydrous ether yielded only the original compound (II).

C. A solution of 5 g. of (II) in 100 ml. of pyridine was saturated with gaseous ammonia below 25° and stirred into a mixture of 150 ml. of concentrated hydrochloric acid, 500 ml. of water, and 500 g. of cracked ice. The dark precipitate which separated was filtered and recrystallized from dilute methanol to yield 3.3 g. of *p*-hydroxyazobenzene as orange-red crystals.

Reaction of compound (II) with 2-aminopyridine. A. In pyridine. To a solution of 22.6 g. of 2-aminopyridine dissolved in 125 ml. of pyridine maintained below 30° was added 68.5 g. of (II) over a period of 10 minutes. A portion of (II) did not dissolve. The mixture was warmed in a water-bath and at approximately 40° all (II) went into solution. The mixture was heated under reflux for 2 hours and allowed to cool. Approximately one-half of the pyridine was distilled under reduced pressure and the residue was triturated with 450 ml. of 1:2 hydrochloric acid and stirred into 1200 ml. of cracked ice and water. The semisolid which separated was allowed to settle overnight, filtered, dissolved in dilute sodium hydroxide, and reprecipitated with carbon dioxide. Recrystallization from dilute methanol gave pure *p*-hydroxyazobenzene.

B. In acetone-pyridine. A solution of 14.8 g. of (II) in 200 ml. of dry acetone was treated successively with 15 ml. of pyridine, 4.7 g. of 2-aminopyridine, and 50 ml. of dry acetone. The mixture was shaken and allowed to stand at room temperature An immediate precipitation of a yellow crystalline solid took place. After standing overnight the precipitate was filtered and washed with dry acetone. The yield was 8.1 g. The product was repeatedly recrystallized from ethanol to give colorless crystals of 2-aminopyridine sulfate melting at 208–210° and not depressing the melting point in mixture with authentic 2-aminopyridine sulfate prepared from 2-aminopyridine and sulfuric acid. The picrate melted at 216–217° and a mixed melting point with the known picrate was not depressed.

The filtrate and washings were distilled under diminished pressure to a small volume and diluted with an excess of water. The dark oil which separated solidified under vigorous agitation. The solid was filtered, washed with water, dissolved in dilute sodium hydroxide, precipitated with hydrochloric acid, and recrystallized from methanol, giving 9.8 g. of *p*-hydroxyazobenzene melting at 150–151°.

Reaction of compound (II) with alkali. A. Ten grams of (II) was placed in a 500-ml 2-neck flask set up for distillation. A solution of 20 g. of sodium hydroxide in 250 ml. of water was added and the mixture was boiled. Water was gradually added from a dropping-funnel to keep the volume constant. The reaction mixture became clear and orange-red in color. A bright orange oil which solidified on cooling distilled with the steam. A yield of 0.8 g. of orange crystals melting at 50–52° was obtained. The clear alkaline solution in the distilling flask was acidified with hydrochloric acid and filtered. The precipitate was recrystallized from methanol to yield 6.0 g. of *p*-hydroxyazobenzene. Treatment of the aqueous filtrate gave a heavy precipitate of barium sulfate, indicating the presence of sodium sulfate in the original alkaline solution. The presence of sodium chloride in the alkaline solution was proved by another identical experiment in which some of the alkaline solution was acidified with nitric acid and treated with silver nitrate. A heavy precipitate of silver chloride formed.

The steam-distillable orange crystals melting at 50–52° were recrystallized repeatedly from 90% ethanol to yield orange chlorine-containing crystals melting at 86–87°. Bamberger (9) reports the melting point 87° for *p*-chloroazobenzene A sample was dissolved in concentrated sulfuric acid, allowed to stand overnight, and diluted with water. The yellow precipitate which separated was recrystallized from ethanol to give crystals melting at 146–147°, which is the melting point of *p*-chloroazobenzenesulfonic acid prepared by Mentha and Heumann (10).

The mother liquors from the above recrystallization were evaporated to dryness and the residue was recrystallized from petroleum ether to give orange plates of azobenzene melting at 65–66° and not depressing a mixed melting point with authentic azobenzene. Reduction with stannous chloride in acid solution or with zinc in alkaline solution and subsequent acid treatment yielded benzidine melting at 124–125°.

B. The above experiment was repeated with concentrated ammonium hydroxide in place of the sodium hydroxide solution. No red oil distilled with the steam. The aqueous solution yielded 6.6 grams of *p*-hydroxyazobenzene Both chloride ions and sulfate ions were identified in the solution

Reduction of compound (II). A solution of 6.5 g. of compound (II) in 150 ml. of purified benzene was treated with 20 g. of alcohol-washed Raney nickel catalyst and shaken with hydrogen at 50 lbs./sq. in. at room temperature. The solution became colorless and hydrogen absorption was complete in 2 hours. The catalyst was removed, and the clear solution was concentrated to a small volume. The residual solution gradually deposited colorless crystals. These were filtered and dried to give *p*-aminophenol melting at 184–185°, no depression in mixture with authentic *p*-aminophenol. Acetylation of the crystals with acetic anhydride gave *p*-aminophenol diacetate melting at 151–152°.

The benzene filtrate from the *p*-aminophenol crystals was refluxed a short time with acetic anhydride in anhydrous pyridine and then concentrated to dryness under reduced pressure on the steam-bath. The product was recrystallized from water to give acetanilide melting at 113–114° and not depressing the melting point of a mixture with authentic acetanilide. This proves that aniline was present in the original hydrogenation solution. The amounts of aniline and *p*-aminophenol were approximately equal.

One-half of the catalyst was washed well with alcohol, to remove any benzene, and the resulting black powder was suspended in water and acidified with dilute hydrochloric acid.

Hydrogen sulfide was liberated in considerable quantity. This indicated that the sulfur in compound (II) was reduced to hydrogen sulfide.

The other half of the catalyst was boiled with benzene and filtered hot. The cooled benzene was shaken with dilute, acidified silver nitrate solution. A precipitate of silver chloride separated, indicating that the chlorine present in the original (II) was reduced to hydrogen chloride.

Ultraviolet absorption. The ultraviolet absorption spectra were measured with a Beckman model DU quartz spectrophotometer employing 1.0-cm. quartz cells and minimum slit widths. Measurements were made on freshly and accurately prepared solutions containing 0.01 g. of compound per liter in purified *n*-heptane. Azobenzene and azoxybenzene were prepared by the reduction of nitrobenzene with sulfite waste liquor and alkali at superatmospheric and atmospheric pressure, respectively (1). Azobenzenesulfonyl chloride was prepared from azobenzene and chlorosulfonic acid (3). All products were repeatedly recrystallized from reagent grade petroleum ether.

SUMMARY

Reaction of azoxybenzene with chlorosulfonic acid yields an anomalous reaction product. On the basis of chemical reactions and ultraviolet absorption spectra, the structure *p*-azobenzene chlorosulfonate has been proposed.

APPLETON, WISCONSIN

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[CONTRIBUTION NO. 15 FROM THE INSTITUTE FOR ATOMIC RESEARCH AND THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

THE PREPARATION OF α-FURILDIOXIME

SHERMAN A. REED, CHARLES V. BANKS, AND HARVEY DIEHL

Received May 2, 1947

The general interest in this laboratory in the use of the 1,2-dioximes in analytical chemistry (1) has naturally lead to a study of the methods of preparation of the various dioximes which have been proposed as analytical reagents. Following the original work of Soule (2) on the use of α-furildioxime as a reagent for nickel, there appear to be only two studies of the analytical applications of this reagent (3, 4). In a large measure this lack of interest derives from the difficulties in the preparation of the material and its consequent high price.

The synthesis of α-furildioxime involves the conversion of furfural to furoin by the acyloin condensation, the oxidation of the latter to furil by copper sulfate in pyridine, and the oximation of the furil. Hartman and Dickey (5) greatly improved the syntheses of furoin and furil but the last step has remained a serious stumbling block. The present paper deals with this last step.

Alpha-furildioxime was prepared by Macnair (6) along with some β-furildioxime by allowing furil to stand for several days or months in an alcoholic solution of hydroxylammonium chloride, and Soule (2) effected the oximation by refluxing an alcoholic solution of furil and hydroxylammonium chloride for five or six hours. Little is said about yield in either paper.

Our results with Soule's procedure were inconsistent and the yields ranged from one to twenty-three per cent. A series of oximations was carried out, varying singly the temperature, reflux time, and excess of hydroxylammonium chloride. No improvement in yield was obtained. Macnair (6) reported that α-furildioxime was converted to the β-form when heated to 150–160°, and that it was partially decomposed when heated in the presence of excess hydrochloric acid. Another series of experiments was conducted in which the excess hydrochloric acid was neutralized with calcium carbonate or sodium bicarbonate prior to removing the methanol, and in which the temperature was held below 90° throughout the procedure. The yields were again poor. Additional preparations were carried out using sodium hydroxylamine monosulfonate as an oximating agent, but these also were unsatisfactory.

Assuming that some side reaction competes seriously with the oximation reaction, it should be possible to favor the oximation by the slow addition of the furil to the hydroxylammonium chloride solution so that the latter is always greatly in excess. This scheme was found to give consistent and greatly increased yields. The details are given in the following recommended procedure.

EXPERIMENTAL

Alpha-furildioxime. In a 5-l. round-bottomed flask place 3200 ml. of technical-grade methanol, 208.5 g. (2.25 moles) of hydroxylammonium chloride, and a few boiling chips. Equip the flask with a 1500-ml. Soxhlet extractor[1] fitted with a suitable reflux condenser.

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[1] Dr. C. F. H. Allen suggested the use of a hot Soxhlet extractor such as is described by Pingert, "Synthetic Organic Chemicals," Eastman Kodak Company, Rochester 4, N. Y., Vol. 18, No. 1, 1946.

Place a mat of glass wool in the bottom of the extractor and charge the extractor with 190 g. (1 mole) of purified furil. Heat the flask (most conveniently with an electric heating mantle and variable transformer) so that the alcohol boils vigorously and the methanol refluxes rapidly enough to fill the extractor at a rate of *ca.* 10 ml. per minute. Wrap a piece of asbestos paper around the siphon tube to prevent the furil from crystallizing in it.

As the extractor fills with methanol, the furil slowly dissolves and upon overflowing, 800 to 900 ml. of saturated alcoholic furil solution is added to the reaction flask. Within 10 to 15 minutes after the first furil has been added, the solution in the flask will turn straw yellow and continue to darken as the reaction proceeds and subsequent furil is added. Increase the heat input as necessary to maintain the reflux rate, but do not allow the temperature of the solution to exceed 95°. Continue the reaction until all of the furil has been transferred to the flask. Finally allow the extractor to fill and remove it and the alcohol in it from the flask. Remove the methanol by distillation under reduced pressure stopping the distillation when 500 to 800 ml. of viscous brown solution remains in the flask. After removing the bulk of the methanol do not allow the temperature to exceed 35°. Pour the reaction mixture into a 5-l. Erlenmeyer flask containing 600 ml. of water heated to 90°. Wash the flask with two 100-ml. portions of hot water. Boil the mixture until the crude tar goes into solution (usually 10–15 minutes). Remove the flask from the hot plate and add 100 to 150 g. of Norit previously boiled with dilute hydrochloric acid and, if it is already available, 3 to 5 g. of α-furildioxime to remove iron. Boil the mixture gently for 10 minutes and filter the boiling solution immediately, using a Büchner funnel and suction. Cool the solution under tap water or in an ice-bath. The solution turns milky and crystals of α-furildioxime separate. Filter the crude product on a Büchner funnel and spread it on wrapping paper to dry at room temperature. To recrystallize the product, if it is not white, dissolve it in the minimum of boiling water and treat with 50 g. of Norit as above. Yield 125–135 g., 54–56%; m p. 84–85°, monohydrate. The melted material loses water and thereafter melts at 166–168°.

AMES, IOWA

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[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY,
UNIVERSITY OF CINCINNATI]

2-THIOFLUORENOL

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AND CLIFFORD P. BARTH

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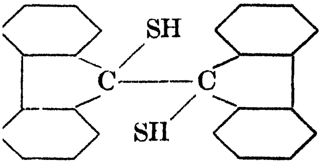
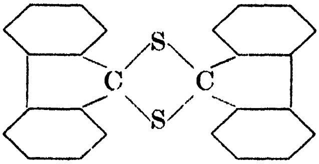
Nearly all of the work on sulfur compounds of fluorene up to present has dealt with derivatives of the 9-carbon atom, although a few aromatic sulfonic acids are known.

Several of the divalent sulfur compounds contain two fluorene nuclei. As early as 1904 Manchot and Krische (1) prepared 9,9'-bifluoryl-9,9'-dithiol, I.



I

In the following year Smedley (2) prepared a compound which she called thiofluorenone and to which she assigned structure II, but Bergmann and Hervey (3) showed that Smedley's compound contained active hydrogens and that its structure should be represented by III. They prepared II by the passage of hydrogen sulfide and hydrogen chloride into fluorenone for 15 hours. Recently Campaigne and Reid (4) obtained monomeric thiofluorenone, IV, by interrupting the process after three hours. They reported it to be an unstable green solid melting at 75–76°. Bergmann and Hervey also prepared 9,9'-difluorylsulfide by the action of sodium hydrosulfide on 9-chlorofluorene.



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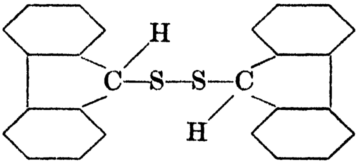

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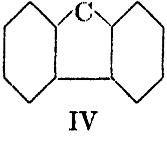
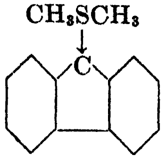


IV

Schonberg, Schutz, and Peter (5) synthesized 9-phenylthiofluorene and the mercaptol type compound, 9-phenylthio-9-*o*-nitrophenylthiofluorene. Several similar mercaptol compounds have been reported (7, 8).

Ingold and Jessup (6) prepared fluorylidenedimethylsulfide, V, which contains a semipolar bond between sulfur and carbon.



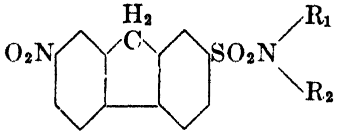
V

Wedekind and Strusser (9) obtained 9-fluorenesulfonic acid from 9-chlorofluorene with sodium bisulfite. Ordinarily, sulfuric acid acts on fluorene to produce first fluorene-2-sulfonic acid, and then fluorene-2,7-disulfonic acid (10, 11, 12).

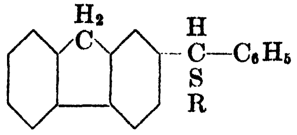
Suter (13) suggests that subsequent sulfonic acid groups would go to positions 3 and 6. Consideration of the nitration products (14), however, makes it seem more probable that the 4 and 5 positions would be involved, as these are ortho to the linkage between the phenyl rings and meta to the first sulfonic acid groups.

Courtot prepared fluorene-2-sulfonyl chloride and the amide (15), as well as 7-nitrofluorene-2-sulfonic acid; while Ray and MacGregor (16) prepared a number of derivatives of the type VI.

Fluorylphenylmethyl thioethers of type VII were used by Ray and Levine (17) in the elucidation of the sulfonium mechanism.

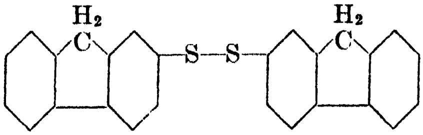


VI



VII

Since 2-thiofluorenol had not been reported, we decided to attempt its preparation. By the reduction of fluorene-2-sulfonyl chloride with iodine and red phosphorus we obtained mostly 2,2′-difluoryl disulfide, VIII, melting at 179–180°, but some low-melting material (m.p. 122°) was isolated also.



VIII

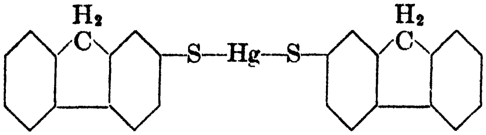
Sodium sulfide failed to reduce the disulfide linkage, while phosphorus pentabromide gave a compound containing bromine in the ring.

With sodium in anhydrous ammonia we obtained a red solid that dissolved in water. On the addition of hydrochloric acid a yellow compound having an indefinite melting point (75–120°) precipitated. This could not be purified to a sharply melting compound and the analytical results were low for 2-thiofluorenol.

The benzoyl derivative, however, melted sharply at 172–173° and gave correct analytical results.

We then turned to the method whereby fluorene-2-sulfonyl chloride was reduced with zinc dust and acetic acid, but the product obtained (m.p. 122°) did not have the expected properties. It was not readily soluble in sodium hydroxide and the analysis for sulfur was 12.86 instead of the calculated 16.15. It did not give a benzoate.

If this compound were the sulfinic acid, mercuric chloride should cause the substitution of HgCl for SO_2H. Instead, when the compound was boiled with mercuric chloride, the mercury salt of 2-thiofluorenol, IX, resulted. It melted at 235–237° and was analytically pure.



IX

To obtain the free thiol, hydrogen sulfide was passed into an alcoholic suspension of the mercury salt. The resulting 2-thiofluorenol melted at 111–113° and the analytical results obtained for sulfur showed it to be somewhat impure. It was, however, readily soluble in alkali, although oxidation soon took place in this medium. Hydrogen peroxide gave the disulfide, VIII, in practically quantitative yields, while the pyridine solution on standing in air gave the disulfoxide.

Inasmuch as we were not completely satisfied with the method of preparation and had not identified the compound originally obtained (m.p. 122°) we decided to prepare 2-thiofluorenol by another method. We treated fluorene-2-diazonium chloride with potassium ethylxanthate and decomposed the addition compound in hot water. On hydrolysis and recrystallization we obtained pure 2-thiofluorenol melting at 129° compared with the previous melting point 111–113°. The mercury salt and the benzoate were identical with those previously obtained. When the thiol was boiled with acetic anhydride, the compound melting at 122° and having 13% sulfur was obtained. It was thus shown to be the acetate, formed by acetylation during the reduction in glacial acetic acid.

EXPERIMENTAL

All melting points uncorrected.

Fluorene-2-sulfonyl chloride was preparėd by Courtot's method (15) but was recrystallized (15 g.) from a mixture (55 cc.) of 3:1 acetic acid-acetic anhydride. It melted at 162°.

Reduction with iodine and phosphorus. Ten grams of fluorene-2-sulfonyl chloride was placed in 300 cc. of 80% acetic acid with 10 g. of red phosphorus and then 8 g. of iodine was added slowly. About 2–3 cc. of concentrated sulfuric acid was added to the mixture after 2 hours. Following 5 hrs. refluxing, the solution was filtered and allowed to stand overnight. An electrophoric powder precipitated. On recrystallization from acetic acid 4.5 g., 60%, of 2,2′-difluoryl disulfide, m.p. 180°, was obtained in the form of a white powder.

Anal. Calc'd for $C_{26}H_{18}S_2$; S, 16.20; Mol. Wt., 394.

Found: S, 16.18, 16.54; Mol. Wt. (benzene), 363.

This compound was also obtained by the oxidation of 2-thiofluorenol with hydrogen peroxide in acetic acid.

Reduction with zinc dust. To 200 cc. of hot anhydrous acetic acid was added 10 g. (0.038 mole) of fluorene-2-sulfonyl chloride. The solution was cooled to 40° and 16 g. (0.24 mole) of zinc dust was added. The temperature rose to 80°. Then 5 cc. of concentrated sulfuric acid was added and the mixture refluxed for an hour. It was filtered, poured into water, and the precipitate recrystallized from alcohol. The fluorene-2-thiol acetate melted at 122° and was soluble in cold benzene, chloroform, and ethyl acetate, and in hot alcohol.

Anal. Calc'd for $C_{15}H_{12}OS$: S, 13.3; Eq. Wt., 240.

Found: S, 12.86; Eq. Wt., 231.

The equivalent weight was determined by boiling for 1 hr. in an excess of standard alkali and then titrating with standard acid.

Fluorene-2-diazonium chloride was prepared from 2-aminofluorene (18, 19). It crystallized in golden-yellow needles melting with decomposition at 120°.

2-Thiofluorenol. Two 800-ml. beakers were placed in an ice-salt bath. One contained a solution of 7 g. of potassium ethylxanthate in 100 cc. of water; in the other, 10 g. of fluorene-2-diazonium chloride was suspended in 200 cc. of water. A few cc. of the diazonium chloride was added to the xanthate solution, and a tan, curdy precipitate formed. This was removed in small quantities from the solution and quickly dropped into a beaker containing 25 cc. of boiling water. Nitrogen was explosively evolved and the resulting product existed as a heavy dark brown oil on the surface of the water. More of the diazonium chloride was added to the potassium ethylxanthate and the process continued as above until all the diazonium salt had reacted. The product was allowed to cool, separated from the water, and dissolved in 250 cc. of ether. It was then washed with four 100-cc. portions of 5% NaOH, two 100-cc. portions of 5% HCl, and two 100-cc. portions of water. After standing overnight over calcium sulfate the ether was evaporated. The dark brown tar was hydrolyzed by refluxing for 5 hours with 15 g. of KOH dissolved in 50 cc. of water and 100 cc. of alcohol. The solution was filtered hot and the alcohol evaporated. The potassium salt of the thiol was a reddish brown powder which readily dissolved in water. On the addition of 25 cc. of dilute sulfuric acid to the water solution, the crude orange colored thiol precipitated. This was filtered by suction and when dry melted at 58–62°. On heating with alcohol, the thiol dissolved leaving a brown tar which was removed. Water was added to the solution bringing down a yellow precipitate which melted at 98°. Several recrystallizations with 150-cc. portions of 2:1 alcohol-water mixtures, and boiling with Darco gave 2.6 g. of a pale yellow product melting at 108-112°. It was difficult to purify the 2-thiofluorenol further; however, after numerous purifications, small white crystals melting at 127–129° were obtained.

Anal. Calc'd for $C_{13}H_{10}S$: S, 16.15; Mol. Wt., 198.

Found: S, 16.06, 16.12; Mol. Wt. (camphor), 185.

Mercury salt of 2-thiofluorenol. Three g. of 2-thiofluorenol was dissolved in 200 cc. of alcohol and filtered hot through a charcoal mat. To this clear solution 3 g. of mercuric chloride in hot alcohol was added, and a bright yellow precipitate resulted. The reaction mixture was cooled with constant shaking over a period of ½ hour; the product melted at 217–219°. After several recrystallizations from Cellosolve, the constant melting point 235–237° was obtained.

Anal. Calc'd for $C_{26}H_{18}S_2Hg$: Hg, 33.71. Found: Hg, 33.41.

Fluorene-2-thiol benzoate. One and one-half g. of 2-thiofluorenol was added to 100 cc. of boiling 6 *N* sodium hydroxide. After boiling for about a minute a soap-like tan substance formed. This was cooled and 5 cc. of benzoyl chloride added with stirring. The solution was filtered and on standing overnight yellow crystals came down. When dry they melted at 142°. After several recrystallizations from ethyl alcohol a product melting at 172–173° was obtained.

Fluorene-2-thiol acetate. Approximately 0.5 gram of 2-thiofluorenol was dissolved in 5 cc. of acetic anhydride and brought to a boil. The solution was cooled in an ice-bath and 5 cc. of 6 *N* sodium hydroxide and a little ice were added. After constant shaking over a period of 15 minutes a yellow precipitate came down (m.p. 102–108°). After several recrystallizations from the minimum of alcohol, a product melting at 120–122° was obtained.

Anal. Calc'd for $C_{15}H_{12}OS$: S, 13.3. Found: S, 12.97.

A mixed melting point with the material obtained by the reduction of fluorene-2-sulfonyl chloride with zinc dust in glacial acetic acid showed them to be identical.

Reduction of 2,2'-difluoryl disulfide. Three grams of the disulfide was dissolved in 150 cc. of anhydrous ammonia and small pieces of metallic sodium added until the characteristic blue color persisted. When the ammonia had evaporated, the mass was dissolved in water and acidified. The crude material was recrystallized from dilute alcohol but could not be obtained pure (m.p. 100–110°).

Anal. Calc'd for $C_{13}H_{10}S$: S, 16.15. Found: S, 15.55.

It was converted to the benzoate with benzoyl chloride and dilute sodium hydroxide. From 1.5 g. of thiol there was obtained 1.3 g. of fluorene-2-thiol benzoate. On recrystallization to the constant m.p. 173°, 1 g. or 65% was obtained.

Anal. Calc'd for $C_{19}H_{14}OS$: S, 10.59. Found: S, 10.28.

2,2'-Difluoryldisulfoxide. One g. of 2-thiofluorenol was boiled with pyridine, filtered, and the clear solution allowed to stand in air for 12 hours. A yellow compound precipitated. On recrystallization from Methyl Cellosolve there was obtained 0.4 g. melting at 217°.

Anal. Calc'd for $C_{26}H_{18}O_2S_2$: S, 15.02; Mol. Wt., 426.
Found: S, 14.90, 14.96; Mol. Wt. (camphor), 468.

SUMMARY

2-Thiofluorenol and its derivatives; the acetate, the benzoate, the mercury salt; and 2,2'-difluoryl disulfide and 2,2'-difluoryldisulfoxide have been prepared and characterized.

2-Thiofluorenol has been prepared both by the reduction of fluorene-2-sulfonyl chloride and by the reaction of fluorene-2-diazonium chloride with potassium ethylxanthate.

CINCINNATI 21, OHIO

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[Contribution from the Noyes Chemical Laboratory,
University of Illinois]

THE SYNTHESIS OF 5-HYDROXY-8-NITROQUINOLINE AND CERTAIN OF ITS DERIVATIVES[1]

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and ELLIOT N. MARVELL[2]

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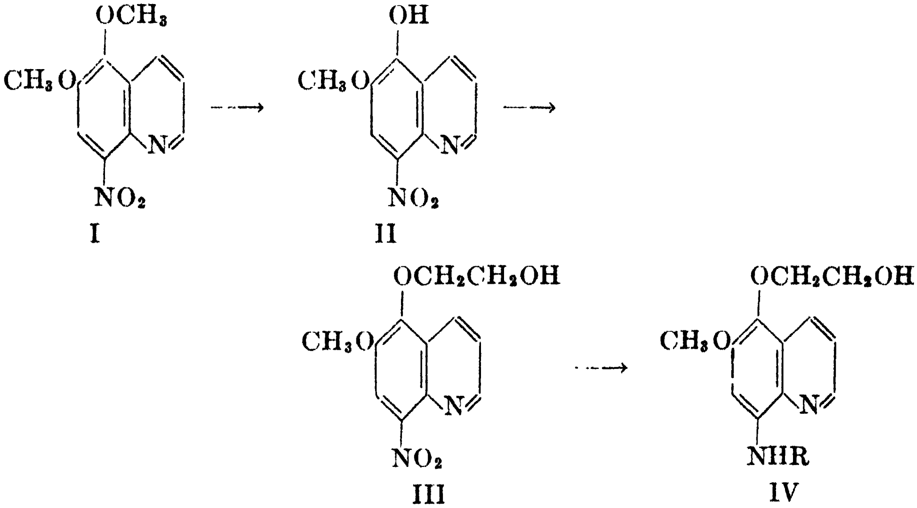
In a search for an antimalarial drug of the plasmochin type which would be less toxic than plasmochin, attention was directed to certain derivatives of 5-hydroxy-8-aminoquinoline. In particular, it was desired to introduce the 2-hydroxyethoxyl group into position 5 of the quinoline ring. Although this investigation was interrupted before any satisfactory candidate drug had been produced, certain of the intermediates had been made. The present paper is a report of this synthetic work.

The original plan for the synthesis of one of the drugs involved the following sequence of transformations.



By analogy with the results of Cardwell and Robinson (1) on the hydrolysis of 4-nitroveratrole, it was expected that cleavage of the 5-methoxyl group in 5,6-dimethoxy-8-nitroquinoline (I) could be effected by use of aqueous ethanolic potassium hydroxide and that acid catalysts would bring about preferential cleavage of the methoxyl group in the 6 position. Experiment showed, however, that when the dimethoxy compound was hydrolyzed by either alkaline or acidic reagents, cleavage occurred at the 5 position only. Heating in a closed tube with concentrated hydrochloric acid was necessary to cleave both methoxyl groups. The ease of cleavage of the 5-methoxyl group was such that it took place slowly when an aqueous methanol solution of the dimethoxyquinoline was boiled for an extended period during recrystallization. The most satisfactory method for obtaining the hydroxy compound (II) was to heat the dimethoxyquinoline with dilute hydrochloric acid.

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[1] The work described in this paper was done in part under a contract, recommended by the National Defense Research Committee and the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

[2] American Chemical Society, Postgraduate Fellow, 1946–47.

The quinolinol (II) was a bright red solid, soluble in dilute acids or bases but insoluble in most organic solvents, and had the melting point 240°. It proved to be very difficult to alkylate, attempts at methylation with methyl sulfate and with diazomethane, for example, being unsuccessful. However, reconversion to the dimethoxyquinoline (I) was accomplished in low yield by the action of methyl iodide on the silver salt of the quinolinol.

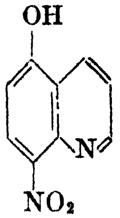
In an effort to evaluate the influence of the methoxyl group on the quinolinol (II) the hitherto unknown 5-hydroxy-8-nitroquinoline (V) was synthesized. It was made from 5-chloro-8-nitroquinoline both by direct hydrolysis and by acid cleavage of the intermediate 5-methoxy-8-nitroquinoline. Preparation and hydrolysis of 2-nitro-5-chloroacetanilide was an essential step in the synthesis of 5-chloro-8-nitroquinoline. Better yields of 2-nitro-5-chloroacetanilide were obtained by nitrating *m*-chloroacetanilide with fuming nitric acid in glacial acetic acid and acetic anhydride than were possible with previous procedures (2, 3, 4). When 2-nitro-5-chloroacetanilide was treated with sodium ethoxide, an almost quantitative yield of the free amine was obtained. This catalytic exchange method was discovered by Verkade (5).

6-Hydroxy-8-nitroquinoline, likewise new, was obtained in low yield by the acid cleavage of the well-known 6-methoxy-8-nitroquinoline.

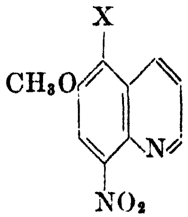
The melting points of all *bz*-hydroxy-8-nitroquinolines are high. 5-Hydroxy-8-nitroquinoline melts with decomposition at 261°, 6-hydroxy-8-nitroquinoline at 242°, and 7-hydroxy-8-nitroquinoline at 255° (6). All these nitroquinolinols are deeply colored; 5-hydroxy-8-nitroquinoline is brilliant yellow, 6-hydroxy-8-nitroquinoline is red-brown, and 7-hydroxy-8-nitroquinoline is bright yellow. Examination of the literature showed that, with many phenolic compounds that can be alkylated only with difficulty, success could be achieved by use of the silver salt and an alkyl iodide. Thus 5-hydroxy-6-methoxy-8-nitroquinoline appears to have properties that are similar to those of other nitroquinolinols of the same type.

The conversion of the quinolinol (II) to the corresponding 2-hydroxyethoxy compound (III) by ethoxylation could not be effected. The action of benzyloxyethyl *p*-toluenesulfonate in ethanolic potassium hydroxide (7) on the quinolinol, of benzyloxyethyl iodide or ethylene bromohydrin on the silver salt of the quinolinol, and of ethylene oxide on the potassium salt of the quinolinol failed to yield the desired derivative.

Tetrakis (2-hydroxyethyl)ammonium hydroxide in 39% aqueous solution was tried also as an alkylating agent. Experiment showed that *p*-nitrophenol, employed as a model compound, could be converted to 2-(*p*-nitrophenoxy)ethanol by use of this reagent. However, attempts to hydroxyethylate the quinolinol were unsuccessful.



V



VI (X = Cl)
VII (X = Br)

The hydroxyethoxy derivative (III) was finally obtained from 5-chloro-6-methoxy-8-nitroquinoline (VI). The chloro compound had been prepared from 4-amino-2-chloro-5-nitroanisole previously by the Skraup reaction (8). In the present work it was found possible to make it in high yields by treating the quinolinol (II) with phosphorus oxychloride. The conversion of the chloro compound to ethers by treatment with sodium alkoxides had been carried out earlier (9). The hydroxyethoxy compound (III) was made by treatment of the chloro derivative (VI) with the monosodium derivative of ethylene glycol. Actually, it was possible to effect this change simply by heating the chlorine derivative with ethylene glycol in the presence of potassium hydroxide and a small amount of water.

The same hydroxyethoxy derivative was obtained when the bromo compound (VII), prepared by the directions of Lauer, Rondestvedt, Arnold, Drake, Van Hook, and Tinker (10), was employed in place of the chloro compound. Since the structure of the bromo compound was known, the identity of the alkylation products from the two halogen compounds confirms the structures assigned to the chloro compound and the quinolinol, and proves that cleavage of the dimethoxy compound took place at position 5 rather than 6.

In the preparation of the hydroxyethoxy derivative it was observed that the two halogen compounds gave approximately the same yields and that the yield was not increased by the addition of potassium iodide. The presence of water was found to be necessary, although it caused a considerable amount of the halogen compound to revert to the quinolinol.

The hydroxyethoxy derivative was much more soluble in water than was the quinolinol. It could be reconverted to the hydroxy compound by hydrolysis with hot 50% aqueous ethylene glycol containing potassium hydroxide.

Reduction of the nitro compound (III) to the amine (IV, R = H) was effected in 84% yield by the use of platinum oxide and hydrogen under a few atmospheres pressure. The alkylation of the amine with 6-diethylamino-1-bromohexane was attempted by fusing the reactants in the absence of a solvent. The product was a yellow oil which when exposed to air rapidly developed a green color which soon turned brown. Attempts to convert the compound to a non-hygroscopic salt suitable for pharmacological testing were unsuccessful.

EXPERIMENTAL[3]

5-Hydroxy-6-methoxy-8-nitroquinoline (II). A. *Alkaline cleavage.* Five grams of 5,6-dimethoxy-8-nitroquinoline, 38 g. of potassium hydroxide, 125 g. of ethanol, and 110 g. of water were heated together at reflux temperature for eighteen hours. At the end of this time, the suspended material originally present had dissolved. When the reaction mixture was cooled, the orange-colored potassium salt of 5-hydroxy-6-methoxy-8-nitroquinoline was deposited. Extraction of the salt with ether and chloroform indicated the absence of 5,6-dimethoxy-8-nitroquinoline. The free 5-hydroxy compound was obtained as a bright red solid by acidification of the alkaline solution with concentrated hydrochloric acid (Congo Red). It was removed by filtration, washed, and dried in an oven. The yield was 3 g. or 64%. A sample was dissolved in alkali, reprecipitated with acid, washed with water and alcohol, and dried. It melted at 233°, with decomposition. The melting point 243–245° has been reported (11).

B. *Acid cleavage.* A mixture of 100 g. of crude 5,6-dimethoxy-8-nitroquinoline, 50 ml. of concentrated hydrochloric acid, and 1000 ml. of water was heated in an oil-bath at reflux temperature for six hours. A few drops of Aerosol-OS (10% solution) were added to prevent excessive foaming during the heating. After the reaction mixture had been cooled to room temperature, the dark red product was washed with water. The crude product was dissolved in a solution of 20 g. of sodium hydroxide in 3.5 l. of warm water, and the orange solution was filtered. The filtrate was made acid to litmus by adding a solution of about 40 ml. of concentrated hydrochloric acid in 500 ml. of water. The bright red product was washed with water, and dried in an oven. The yield was 89.6 g. (95%); m.p. 236–238°, with decomposition.

Alkylation of 5-hydroxy-6-methoxy-8-nitroquinoline. A. *With methyl iodide.* The silver salt of 5-hydroxy-6-methoxy-8-nitroquinoline was prepared by dissolving 3 g. of the 5-hydroxy compound in dilute sodium hydroxide and adding an aqueous solution containing 2.3 g. of silver nitrate. The red precipitate was washed well with water; the dry solid weighed 4 g. To a mixture of equal weights of the silver salt and methyl iodide was added 6 ml. of methanol, and the mixture maintained at reflux temperature for four hours. Excess methanol was added and the mixture filtered. The residue from the filtration was extracted several times with hot methanol; the extracts were combined with the above filtrate and evaporated to dryness under reduced pressure. The residue obtained by evaporation was taken up in ether; the ether solution was washed once with water, twice with 10% sodium hydroxide solution, and once again with water. Evaporation of the ether left light yellow needles; m.p. 123–125°. The melting point of a mixture of this product with authentic 5,6-dimethoxy-8-nitroquinoline was not depressed; the yield was 0.27 g. or 8.5%.

5-Chloro-6-methoxy-8-nitroquinoline. Phosphorus oxychloride (150 ml.) was heated in an oil bath to 80° and 41 g. of 5-hydroxy-6-methoxy-8-nitroquinoline was added slowly with vigorous stirring. After the addition was complete, the mixture was brought to reflux temperature, and heating and stirring were continued one and one-half hours. The cooled mixture was poured into 700 ml. of concentrated ammonium hydroxide, sufficient ice being added to prevent the temperature from rising above 25°. The precipitate was washed with water, and dried in an oven. The cream-colored solid, m.p. 203.5–205°, weighed 42 g. (95%); the melting point 204° has been reported (8).

5-(2-Hydroxyethoxy)-6-methoxy-8-nitroquinoline. A. *By use of monosodium glycolate.* To a solution of 0.5 g. of sodium metal in 12 ml. of absolute ethanol was added 1.25 g. of ethylene glycol. The ethanol was removed *in vacuo*, and 50 ml. of ethylene glycol was added as solvent. The mixture was heated nearly to boiling, and 4.77 g. of 5-chloro-6-methoxy-8-nitroquinoline was added with stirring. After the heating had been continued for two hours, the reaction mixture was cooled and poured into 350 ml. of water. After filtration to remove a black solid, the solution was extracted with two 100-ml. portions of ether.

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[3] All melting points are corrected.

After the combined ether extracts were dried over Drierite, the ether was removed and the yellow residue (m.p. 110–150°) was recrystallized three times from a benzene-ligroin mixture, Darco being used during the first recrystallization. The 5-(2-hydroxyethoxy)-6-methoxy-8-nitroquinoline was a bright yellow solid melting at 122–123°.

Anal. Calc'd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58.
Found: C, 54.74; H, 4.36.

The acetyl derivative, prepared by treating the amine with acetic anhydride and pyridine and crystallized from dilute methanol, had a pale yellow color and melted at 70–71°.

Anal. Calc'd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61.
Found: C, 55.20; H, 4.60.

B. *By use of ethylene glycol and potassium hydroxide.* To a suspension of 2.4 g. of 5-chloro-6-methoxy-8-nitroquinoline in 96 ml. of ethylene glycol was added a solution of 0.66 g. of 85% potassium hydroxide in 10 ml. of water. The mixture was heated for five hours at 165° and then concentrated nearly to dryness by distillation under water-pump pressure. Extraction with 100 ml. of boiling water removed the hydroxyethoxy derivative, leaving behind 0.41 g. (m.p. 197–200°) of starting material. After the water solution had been treated with Darco it was allowed to cool. The hydroxyethoxy derivative crystallized in greenish-yellow needles weighing 0.82 g.; m.p. 119–121°; yield 32%.

Similar results were obtained when the bromo compound (VII) was employed. The addition of potassium iodide did not affect the yield appreciably. In addition to the hydroxyethoxy compound and the unchanged halogen compound, some hydroxyquinoline (II) was formed.

8 Amino-5-(2-hydroxyethoxy)-6-methoxyquinoline. A mixture of 7.1 g. of 5-(2-hydroxyethoxy)-6-methoxy-8-nitroquinoline, 150 ml. of absolute ethanol, and 0.15 g. of platinum oxide catalyst was subjected to a hydrogen pressure of 40 lb. per sq. in. in an Adams apparatus. The theoretical amount of hydrogen was absorbed in thirty-five minutes. After removal of the catalyst, the hot alcohol solution was treated with Norit and a pinch of sodium hydrosulfite. The filtrate was concentrated by distillation and again treated with Norit and sodium hydrosulfite. Low-boiling petroleum ether (b.p. 30–60°) was added to incipient cloudiness, and the mixture was allowed to stand in an ice-box. The tan-colored needles which formed were washed with a benzene-petroleum ether mixture. The dry product, m.p. 103–104°, weighed 4.93 g. Concentration of the mother liquor and treatment as above yielded 0.34 g. of product; m.p. 103–106°. The total yield was 84%. A sample recrystallized from water had the melting point 104–105°.

Anal. Calc'd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 6.02.
Found: C, 61.63; H, 5.76.

The picrate was prepared by dissolving the amine in 95% ethanol and treating with a saturated ethanolic solution of picric acid. A sample recrystallized from absolute ethanol melted at 174–176°.

Anal. Calc'd for $C_{18}H_{17}N_5O_{10}$: C, 46.67; H, 3.69.
Found: C, 46.73; H, 3.49.

2-[8-(6-Diethylaminohexylamino)-6-methoxy-5-quinolyloxy]ethanol. An intimate mixture of 9.53 g. of 8-amino-5-(2-hydroxyethoxy)-6-methoxyquinoline and 12.9 g. of 6-diethylamino-1-bromohexane hydrobromide was heated in an oil-bath, with stirring, at 115–125° for twelve hours and at 125–135° for two hours, nitrogen being admitted continuously above the reaction mixture. The brittle, red solid obtained by cooling the reaction mixture was dissolved in approximately 150 ml. of warm water. After the aqueous solution had been cooled in ice, it was made strongly alkaline to litmus with 20% sodium hydroxide solution and extracted three times with chloroform (U.S.P.). The aqueous layer was partially saturated in the cold with potassium carbonate and extracted twice with chloroform. After the chloroform solution had been dried over magnesium sulfate, the solvent was removed and the residue subjected to distillation under the vacuum of an oil-pump and a liquid air-charcoal trap. A small forerun was collected as a yellow oil; b.p. 150–160° (0.1–0.3 mm.). A sample of the unstable oil was analyzed immediately.

Anal. Calc'd for $C_{22}H_{35}N_3O_3$: C, 67.83; H, 9.06.
Found: C, 68.93; H, 8.21.

5,6-Dihydroxy-8-nitroquinoline hydrochloride. A solution of 2 g. of crude 5,6-dimethoxy-8-nitroquinoline in 30 ml. of concentrated hydrochloric acid in a sealed tube was heated at 150° for six hours. The dark red crystals which were obtained were washed with concentrated hydrochloric acid; weight 1.4 g. A sample was prepared for analysis by recrystallizing four times from 95% ethanol to which ethyl ether had been added after filtration. The bright orange, water-soluble hydrochloride melted with decomposition at 233–238° in a sealed tube.

Anal. Calc'd for $C_9H_6N_2O_4.HCl$: C, 44.35; H, 2.91.
Found: C, 43.85; H, 2.73.

2-Nitro-5-chloroacetanilide. A solution of 17 g. of *m*-chloroacetanilide in a mixture of 20 g. of acetic anhydride and 9 g. of acetic acid was cooled to 0°. The temperature was held carefully within the limits 0° to −5° while a mixture of 9 g. of acetic acid and 10 g. of nitric acid (sp. gr. 1.52) was added slowly. The clear liquid, after being allowed to stand overnight at room temperature, was poured on 400 g. of crushed ice. The precipitate was washed thoroughly with water, and dried *in vacuo*. The dry solid was triturated with two 100-ml. portions of dry benzene and the insoluble 3-chloro-4-nitroacetanilide removed. The 2-nitro-5-chloroacetanilide, obtained by evaporating the benzene solution to dryness was recrystallized from 95% ethanol. The yield was 11.0 g. or 60%; m.p. 117–118°. The melting point 117–118° has been reported for this compound (4).

2-Nitro-5-chloroaniline. A solution of 0.04 g. of metallic sodium in 150 ml. of absolute methanol was added to 12.8 g. of 2-nitro-5-chloroacetanilide and the solution was boiled under reflux for three hours, after which 125 ml. of solvent was removed by distillation. The free amine crystallized in golden leaflets; evaporation of the mother liquor produced a second crop of crystals. The yield of pure amine (m.p. 127.5–128°) was 10 g. or 96%. The melting point 124–125° has been reported for this compound (3).

5-Chloro-8-nitroquinoline. This compound was prepared from 2-nitro-5-chloroaniline by the Skraup reaction according to the directions of Fourneau, Trefoul, Trefoul, and Wancolle (2).

5-Methoxy-8-nitroquinoline. A solution of 3 g. of 5-chloro-8-nitroquinoline and 3 g. of sodium methoxide in 125 ml. of absolute methanol was maintained at 55–60° for six hours and then allowed to stand at room temperature overnight. A yellow, crystalline product was removed from the cold solution, and the filtrate evaporated to dryness in a stream of dry air. The residue was extracted with 10 ml. of distilled water and the insoluble portion combined with the first crop of crystals. After recrystallization from methanol the yellow crystals melted at 119.5–120°. The yield of 5-methoxy-8-nitroquinoline was 2.5 g. or 85%.

Anal. Calc'd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95.
Found: C, 59.06; H, 3.77.

5-Hydroxy-8-nitroquinoline. A. *By cleavage of 5-methoxy-8-nitroquinoline.* A solution of 1 g. of 5-methoxy-8-nitroquinoline in 50 ml. of distilled water and 3 ml. of concentrated hydrochloric acid was boiled under reflux for six hours, and then allowed to stand overnight at room temperature. Enough dilute sodium hydroxide solution was added to make the solution weakly acid to Congo Red paper, the solid precipitate was dissolved in dilute sodium carbonate solution, and the insoluble 5-methoxy-8-nitroquinoline removed. In this way 0.25 g. of starting material was recovered unchanged. The yellow sodium carbonate solution was acidified with acetic acid; the light yellow precipitate, 5-hydroxy-8-nitroquinoline, m.p. 261° (decomp.), weighed 0.61 g.; yield 89% (based on the 5-methoxy-8-nitroquinoline utilized). It crystallized from absolute ethanol as compact orange crystals.

Anal. Calc'd for $C_9H_6N_2O_3$: C, 56.85; H, 3.18.
Found: C, 56.60; H, 3.26.

B. *By hydrolysis of 5-chloro-8-nitroquinoline.* A mixture of 0.5 g. of 5-chloro-8-nitroquinoline, 1.5 g. of potassium hydroxide, 10 ml. of 95% ethanol, and 15 ml. of distilled water was boiled under reflux for seven hours. The clear solution was added to 25 ml. of 95%

ethanol and cooled in the refrigerator. The potassium salt of 5-hydroxy-8-nitroquinoline, obtained as long orange needles, was redissolved in distilled water and treated with acetic acid. The brilliant yellow product was dried in air; the yield was 0.21 g. or 45%; m.p. 258–260° (decomp.).

Acetate of 5-hydroxy-8-nitroquinoline. A solution of 0.61 g. of 5-hydroxy-8-nitroquinoline, 0.5 g. of acetic anhydride, and 25 ml. of dry pyridine was maintained at 70° for four hours and allowed to stand at room temperature overnight. The pyridine and acetic acid were removed by distillation *in vacuo*, and the residue was taken up in ether. Evaporation of the ether produced a fluffy, yellow solid which was recrystallized from petroleum ether (b.p. 80–100°). The acetate, in the form of white needles, was obtained in nearly quantitative yield; m.p. 114–114.5°. It was found to be sensitive to moisture.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.46.
Found: C, 57.10; H, 3.36.

6-Hydroxy-8-nitroquinoline. One gram of 6-methoxy-8-nitroquinoline, 15 ml. of 42% hydrobromic acid, and 7.5 ml of glacial acetic acid were heated in an oil-bath at 140° for forty hours. The dark brown solution was cooled in the refrigerator and the brown crystals isolated on a filter. The filtrate was made neutral to Congo Red paper with 10% sodium hydroxide solution and the brown precipitate collected. When the two solids were combined and extracted with 10% sodium hydroxide solution, an insoluble portion (starting material) weighing 0.25 g. remained. The solution was made acid with acetic acid and the brown powder recrystallized from ethanol; brown needles, m.p. 242° (decomp.); weight 0.28 g.; yield 40% (based on the 6-methoxy-8-nitroquinoline utilized).

Anal. Calc'd for $C_9H_6N_2O_3$: C, 56.85, H, 3.18.
Found: C, 57.12; H, 3.35.

Acetate of 6-hydroxy-8-nitroquinoline. A mixture of 0 15 g. of 6-hydroxy-8-nitroquinoline, 5 ml. of dry pyridine, and 10 drops of acetic anhydride was allowed to stand overnight at room temperature. The pyridine and acetic acid were removed by distillation *in vacuo*, and the product was recrystallized from a benzene-petroleum ether (b.p. 80–100°) mixed solvent. A nearly quantitative yield of white, needle-like crystals of the acetate was obtained; m.p. 111.5–112°.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.46.
Found: C, 56.88; H, 3.56.

SUMMARY

5-Hydroxy-6-methoxy-8-nitroquinoline has been prepared by the hydrolysis of 5,6-dimethoxy-8-nitroquinoline and converted to 5-chloro-6-methoxy-8-nitroquinoline by the action of phosphorus oxychloride. The chloride and the analogous bromide were converted to the corresponding 2-hydroxyethoxy derivative by treatment with ethylene glycol in the presence of potassium hydroxide. Reduction of the resulting nitro compound yielded 8-amino-5-(2-hydroxyethoxy)-6-methoxyquinoline. Alkylation of the amine with 6-diethylamino-1-bromohexane yielded a compound which appeared to be an impure sample of 2-[8-(6-diethylaminohexylamino)-6-methoxy-5-quinolyloxy]ethanol.

For purposes of comparison, 5- and 6-hydroxy-8-nitroquinoline were synthesized.

URBANA, ILLINOIS

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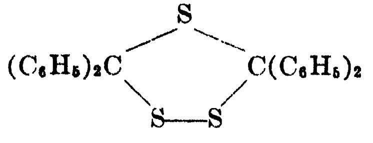
[Contribution from the Chemistry Laboratory of Indiana University]

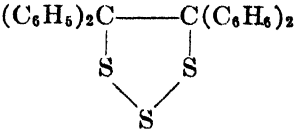
THIOCARBONYLS. IV. THE STRUCTURE OF DIFLUORYL TRISULFIDE AND DIBENZOPHENONE TRISULFIDE[1]

E. CAMPAIGNE and WM. BRADLEY REID, Jr.[2]

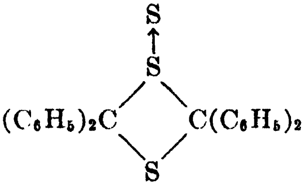
Received May 26, 1947

When thiobenzophenone was exposed to the action of dry air for a long time it was partially converted to a trisulfide having the formula $C_{26}H_{20}S_3$ (1, 2). When this trisulfide was heated above its melting point, it was quantitatively converted to thiobenzophenone and sulfur. Two possible structures, I and II, were suggested for this compound.


I


II

Structure I is most probable, since a compound of structure II would be likely to form tetraphenylethylene rather than thiobenzophenone on heating. A third possible structure, III, containing the dative sulfur atom, might also be considered.


III

Thiofluorenone also yielded a yellow trisulfide of unknown structure, having the formula $C_{26}H_{16}S_3$, after long exposure to air (3).

These two compounds are probably members of the same series, the important characteristic of which is the arrangement of the sulfur atoms, illustrated in formulas I, II, and III. Formula III was readily eliminated on the basis of two simple reactions. Neither the dibenzophenone trisulfide nor the difluoryl trisulfide showed any labile sulfur by the lead acetate test (4), a characteristic of the dative sulfur bond. Both compounds were soluble in hot concentrated alkali, but insoluble in cold alkali, indicating the presence of a disulfide link (5) which is found in either I or II, but not in III. Furthermore, parachor and viscosity measurements on trisulfides and polysulfides indicate that the dative sulfur atom is not found in compounds having less than three sulfur atoms in a linear arrangement (6).

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[1] Taken from part of the thesis submitted by Wm. Bradley Reid, Jr. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University. Presented before the Organic Division at the 110th meeting of the American Chemical Society in Chicago, Illinois, September, 1946. For the third paper of this series, see *J. Am. Chem. Soc.*, **69**, 1211 (1947).

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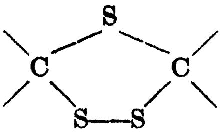
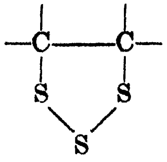
It was therefore necessary to devise experiments which would distinguish between structures A and B.



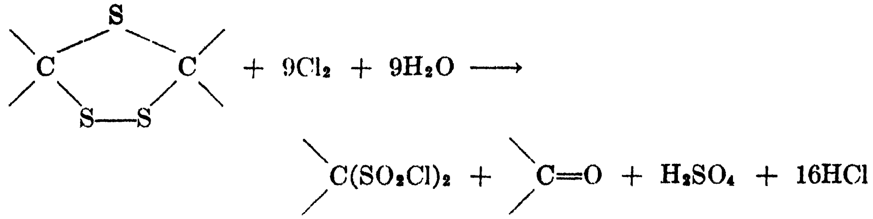
A



B

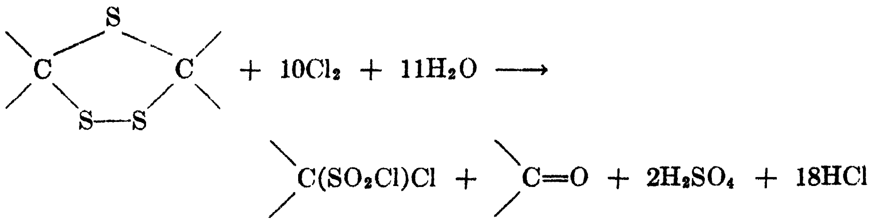
Recently Lee and Dougherty (7) oxidized methylene disulfides to sulfonyl chlorides and formaldehyde. A study of the possible equations for the reaction of chlorine and water on the trisulfide showed that a quantitative estimate of the products of the reaction would indicate the structure of the sulfur-carbon ring. Thus, if structure A is the correct one, the reaction may be written in three possible ways. (Equations 1, 2, and 3).

1.



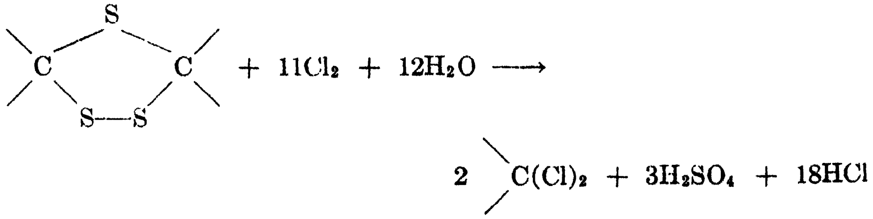
$$+ 9Cl_2 + 9H_2O \longrightarrow C(SO_2Cl)_2 + C{=}O + H_2SO_4 + 16HCl$$

2.



$$+ 10Cl_2 + 11H_2O \longrightarrow C(SO_2Cl)Cl + C{=}O + 2H_2SO_4 + 18HCl$$

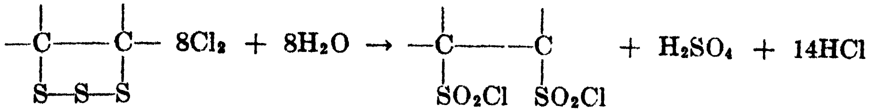
3.



$$+ 11Cl_2 + 12H_2O \longrightarrow 2\,C(Cl)_2 + 3H_2SO_4 + 18HCl$$

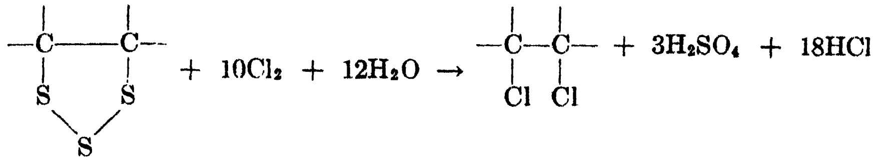
The path of the reaction in this case may be determined by isolation of the disulfonyl chloride, chlorosulfonyl chloride, or ketodichloride, as the case may be, and by determination of the molar ratio of sulfuric acid produced.

If, however, the compound has ring structure B, one mole each of disulfonyl chloride and sulfuric acid should be formed for each mole of trisulfide oxidized, as in equation 4.

4. 

$$\underbrace{-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-}_{S-S-S}\ 8Cl_2 + 8H_2O \rightarrow -\overset{|}{\underset{SO_2Cl}{C}}-\overset{|}{\underset{SO_2Cl}{C}} + H_2SO_4 + 14HCl$$

Since ethane-1,2-disulfonyl chlorides are somewhat unstable, readily losing sulfur dioxide (8), and benzylsulfonyl chlorides also lose sulfur dioxide at slightly elevated temperatures (9), it would seem possible that a 1,2-disulfonyl chloride having phenyl or bis-diphenylene groups attached to the two carbon atoms would lose sulfur dioxide to give a dichloride. The liberated sulfur dioxide would be oxidized to sulfuric acid by free chlorine. Therefore structure B might yield an ethane-1,2-dichloride, as in equation 5.

5. 

$$\underbrace{-\overset{|}{\underset{\underset{S}{|}}{C}}-\overset{|}{\underset{\underset{S}{|}}{C}}-}_{S} + 10Cl_2 + 12H_2O \rightarrow -\overset{|}{\underset{Cl}{C}}-\overset{|}{\underset{Cl}{C}}- + 3H_2SO_4 + 18HCl$$

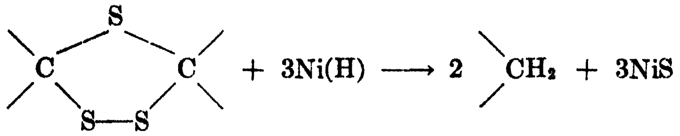
When the dibenzophenone trisulfide was treated with chlorine gas and water in cold glacial acetic acid for two hours, 1.96 moles of benzophenone dichloride per mole of trisulfide was isolated and identified by conversion to benzophenone by hydrolysis. In addition, 2.94 moles of sulfuric acid, determined as barium sulfate, was isolated per mole of trisulfide.

The treatment of the difluoryl trisulfide with chlorine gas and water likewise yielded 2.91 moles of sulfate per mole of trisulfide; however, the fluorene moiety was chlorinated during the reaction and 1.98 moles of an x,9,9-trichlorinated fluorene per mole of trisulfide was isolated. This trichlorinated product yielded a chlorofluorenone on hydrolysis, showing that approximately two moles of keto-dichloride was formed per mole of trisulfide in this reaction also.

The data are in accordance with the structure represented by A and with equation 3. However, Gomberg and Bachmann (10) have shown that the carbon-to-carbon bond of benzpinacol is cleaved by halogens or oxygen. Therefore, it would be possible for the carbon-to-carbon bond in the ethane-1,2-disulfonyl chloride which would be obtained from structure B (equation 4) to be cleaved similarly under the conditions of the reaction, to yield the keto-dichlorides actually obtained.

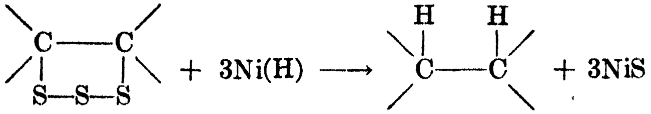
Recently Mozingo, Wolf, Harris, and Folkers (11) described the preparation of Raney nickel containing a large amount of adsorbed hydrogen which is useful in the reductive desulfurization of sulfur compounds. However, under certain conditions nickel has been found to cause coupling with sulfur compounds of the thiocarbonyl type (12, 13). In order to test the usefulness of this reagent on compounds of the type under investigation, dithiofluorenone (IV) was refluxed in an alcohol-benzene mixture with the nickel preparation, and 82% of the theoretical amount of fluorene (V) was obtained. The results of this experiment indicated that this reaction would be applicable to compounds having structure A or B. If the structure of the trisulfides was represented by A, the product of the reaction with Raney nickel would be diphenylmethane or fluorene (equation 6).

6.



However, if B represents the correct structure, then tetraphenylethane or bisdiphenyleneethane should be produced (equation 7).

7.

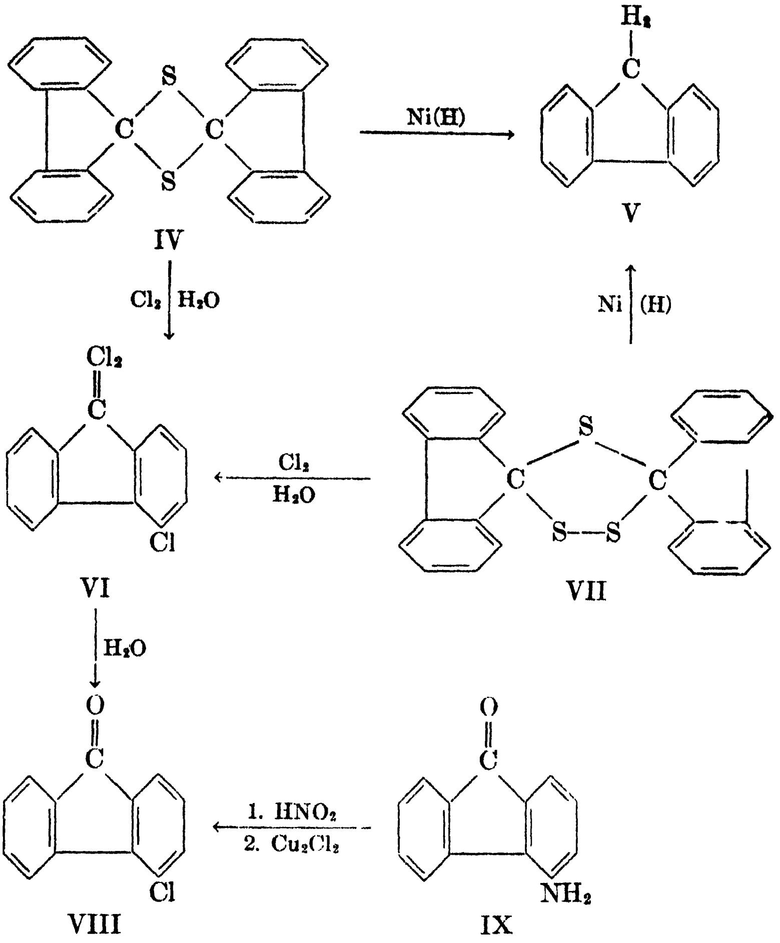


Treatment of the dibenzophenone trisulfide with the nickel preparation gave an 85% conversion to diphenylmethane, which was isolated and identified by physical constants and oxidation to benzophenone. The difluoryl trisulfide was converted by similar treatment to fluorene in rather low yield.

On the basis of these oxidation and reduction studies, the trisulfides formed when thiobenzophenone and thiofluorenone are exposed to the action of dry air are respectively 3,3,5,5-tetraphenyldimethylene-1,2,4-trisulfide, (I), and 3,5-bis-diphenylenedimethylene-1,2,4-trisulfide (VII).

The x,9,9-trichlorofluorene, that was isolated from the reaction of chlorine gas and water on 3,5-bis-diphenylenedimethylene-1,2,4-trisulfide (VII) was also obtained when dithiofluorenone (IV) was treated with chlorine gas and water. This compound had the same melting point as a trichlorofluorene of unknown structure obtained by Holm (14) by treating fluorene dissolved in carbon disulfide with chlorine gas. When the compound was hydrolyzed in dilute hydrochloric acid an x-chlorofluorenone, melting at 145–147°, was obtained, thus showing that two of the chlorine atoms were present as a keto-dichloride. The position of the third chlorine atom was predicted to be in either the 2- or 4- position of the fluorene nucleus, since these are the ortho and para positions to the biphenyl linkage, and meta to the carbonyl group of this compound. However, 2-chlorofluorenone is known to melt at 121–123°, having previously been prepared by Courtot (15).

The previously unknown 4-chlorofluorenone (VIII) was therefore synthesized from 4-aminofluorenone (IX), by the same series of reactions used by Huntress, Pfister, and Pfister (16) for the unequivocal synthesis of 4-bromofluorenone, and found to melt at 146–147°. A mixed melting point of the x-cholorofluorenone with VIII showed no depression, showing conclusively that treatment of dithiofluorenone and 3,5-bis-diphenylenedimethylene-1,2,4-trisulfide with chlorine gas and water yields 4,9,9-trichlorofluorene (VI).



EXPERIMENTAL

The action of chlorine gas and water on 3,3,5,5-tetraphenyldimethylene-1,2,4-trisulfide. One gram (0.00234 mole) of this trisulfide, prepared from thiobenzophenone according to the method of Staudinger and Freudenberger (1), was suspended in 20 ml. of glacial acetic acid and 0.504 g. (0.027 mole) of distilled water was added. Chlorine gas was bubbled through this suspension, and the mixture shaken until the suspended material had dissolved. The temperature of the mixture was kept below 25° during the addition of the chlorine. About fifteen minutes were required for solution of the suspension, after which the yellow solution was allowed to stand for two hours, and then poured over ice and immediately extracted with ether. The ether layer was dried over magnesium sulfate, filtered, and evaporated *in vacuo*. The colorless oil thus obtained gave an immediate precipitate of silver chloride when treated with aqueous silver nitrate solution. This oil was hydrolyzed by heating with water and acetic acid, and the hydrolysate extracted with ether. Evaporation of the dried ether solution gave 0.83 g. of a solid compound, which on recrystallization from alcohol yielded white needles, m.p. 46–47°. A mixed melting point with authentic benzophenone was 46–47°. The yield of crude benzophenone was 97.8%, based on equation 3.

When the aqueous layer was treated with excess barium chloride 1.60 g. of barium sulfate was obtained, which is equivalent to 0.675 g. of sulfuric acid or 98%, based on equation 3.

The action of chlorine and water on 3,5-bis-diphenylenedimethylene-1,2,4-trisulfide. A suspension of 1 g. (0.00224 mole) of the trisulfide prepared from thiofluorenone (3) in 25 ml. of glacial acetic acid containing 0.504 g. (0.027 mole) of water was cooled in an ice-bath. Chlorine gas was introduced until the suspension had just dissolved, after which the reaction mixture was allowed to stand for one hour. The resulting clear yellow solution was poured into a mixture of ice and water and immediately extracted with ether. The ether layer was dried over magnesium sulfate and the ether removed *in vacuo.* A pale yellow solid resulted which weighed 1.2 g., gave an elemental analysis for chlorine, and melted over a wide range. Recrystallization from absolute alcohol gave a yellow crystalline compound, m.p. 147–148° which contained chlorine but gave no test for sulfur.

Anal. Calc'd for $C_{13}H_7Cl_3$: Cl, 39.46. Found: Cl, 39.17.

The crude yield was 99% on the basis of a trichlorofluorene.

The aqueous layer was treated with excess barium chloride, and 1.52 g. of barium sulfate was isolated, which is equivalent to 0.629 g. of sulfuric acid, or 97% based on equation 3.

The action of chlorine and water on dithiofluorenone. Chlorine gas was bubbled through a suspension of 0.5 g. (0.001275 mole) of dithiofluorenone (3) in 8 ml. of glacial acetic acid and 0.184 g. (0.013 mole) of water while the temperature was maintained at 20° for seven hours. The flask was then stoppered and shaken on a shaking machine until solution had taken place. The resulting solution was poured over ice and the yellow precipitate was filtered, washed with cold water, and dried over calcium chloride in a vacuum desiccator. Recrystallization from acetic acid and alcohol yielded a yellow crystalline compound melting at 147–148°. A mixed melting point with the trichlorofluorene obtained from 3,5-bis-diphenylenedimethylene-1,2,4-trisulfide showed no depression.

Hydrolysis of the trichlorofluorene. Four-tenths gram of the trichloride was boiled in a mixture of 5 ml. of acetic acid, 1 ml. of concentrated hydrochloric acid, and 15 ml. of water for four hours. An orange oil formed which solidified on standing. Several recrystallizations from alcohol gave a yellow crystalline compound, m.p. 145–147°, which was shown to be a ketone by a positive 2,4-dinitrophenylhydrazine test, and gave a positive test for chlorine. A mixed melting point with an authentic sample of 4-chlorofluorenone showed no depression.

A 2,4-dinitrophenylhydrazone of this ketone was prepared from 0.1 g. of the ketone by the usual procedure. This reaction yielded 0.185 g. (94%) of microscopic orange crystals, melting at 254–255°.

Anal. Calc'd for $C_{19}H_{11}ClN_4O_4$: N, 14.19. Found: N, 13.99.

A mixed melting point of this 2,4-dinitrophenylhydrazone with one prepared from an authentic sample of 4-chlorofluorenone showed no depression.

The action of Raney nickel on dithiofluorenone. In a 25-ml. round-bottom flask fitted with an efficient reflux condenser, 0.2 g. (0.00051 mole) of dithiofluorenone was treated with about 5 g. of Raney nickel in a mixture of absolute alcohol and sufficient benzene to dissolve the dithiofluorenone when hot. The Raney nickel was prepared according to the method of Mozingo, Wolf, Harris, and Folkers (11). After refluxing for six hours, the nickel and nickel sulfide were removed by filtration, washed with 10 ml. of benzene, and the combined filtrate and washings were placed in a separatory funnel, washed with distilled water, and finally dried over anhydrous calcium sulfate. The dry benzene solution was concentrated *in vacuo* to about 5 ml., and finally transferred to a 15 ml. weighed centrifuge tube with the aid of 5 ml. of dry benzene. Removal of the remaining benzene yielded 0.16 g. of dry solid which on recrystallization from 95% alcohol yielded 0.14 g. or 82.5%, of fluorene, m.p. 114–116°. A mixed m.p. with an authentic sample of fluorene showed no depression.

The action of Raney nickel on 3,3,5,5-tetraphenyldimethylene-1,2,4-trisulfide. In a 250-ml. flask fitted with a reflux condenser, 1 g. (0.00234 mole) of the dibenzophenone trisulfide dissolved in 70 ml. of absolute alcohol and 25 ml. of benzene was treated with 10 g. of the Raney nickel preparation. After six hours of refluxing, the nickel residue was removed by filtration, washed with 25 ml. of benzene, and the filtrate dried over calcium chloride. The solvents were removed by distillation, and the remaining small residue transferred to a 2 ml. modified Claissen flask. The fraction that distilled between 259–263° weighed 0.67 g., which is equivalent to 85% of the theoretical amount of diphenylmethane possible. The liquid has an orange-like odor and an n_D^{23} of 1.5732. Authentic diphenylmethane has a similar odor, boils at 263°, and the refractive index, n_D^{23} is 1.5760. Further proof of the authenticity of the product was secured by oxidizing 0.3 g. (0.0018 mole) with 0.2 g. of chromic anhydride in 2 ml. of glacial acetic acid contained in a 15-ml. centrifuge tube. After two hours of refluxing the resulting dark green solution was diluted with 10 ml. of water, allowed to stand for three hours, centrifuged, and the supernatant liquid decanted. The residual white solid was washed with water, centrifuged, and recrystallized from dilute alcohol. The yield of white needles was 0.15 g. or 45%, m.p. 46–47°. A mixed m.p. with authentic benzophenone showed no depression.

The action of Raney nickel on 3,5-bis-diphenylenedimethylene-1,2,4-trisulfide. When the difluoryl trisulfide was refluxed with Raney nickel, as above, no pure products could be isolated. However, when a solution of 0.5 g. (0.00112 mole) of the trisulfide in 50 ml. of dioxane was shaken at room temperature with 6 g. of Raney nickel for twelve hours, filtered, and the filtrate and dioxane washings concentrated, a brown solid was obtained. Repeated crystallizations of this residue (with 95% alcohol) yielded about 0.05 g. of fluorene, m.p. 114–116°. A mixed m.p. with authentic fluorene showed no depression.

4-Chlorofluorenone. 4-Aminofluorenone was prepared from 2,2′-diphenic acid[3] by the method described by Huntress, Pfister, and Pfister (16). 2,2′-Diphenic acid was converted to fluorenone-4-carboxylic acid, and this compound in turn converted to the amide, and finally to the amine by the Hofmann degradation in an over-all yield of 32% based on the diphenic acid used. The sludge resulting from the addition of 2.72 g. (0.0139 mole) of 4-aminofluorenone to 20 ml. of concentrated hydrochloric acid was cooled to 0° in a salt-ice bath. The mixture was diazotized with a solution of 0.98 g. (0.014 mole) of sodium nitrite in 5 ml. of water. The diazotized solution was then added in a steady stream to a boiling solution of cuprous chloride dissolved in hydrochloric acid. After addition of the diazotized solution, the suspension of orange-yellow material was boiled for fifteen minutes, collected by suction filtration, and washed with cold water. The residue on the funnel was ground with a solution of 8 g. of sodium hydroxide in 25 ml. of water and the undissolved ketone filtered, washed free of alkali, and air-dried. The crude ketone was distilled in vacuum and the fraction that distilled to 160° at 1 mm. was twice recrystallized from absolute alcohol. The yield of long yellow needles, m.p. 147–148°, was 0.75 g. or 25%.

Anal. Calc'd for $C_{13}H_7ClO$: Cl, 16.53. Found: Cl, 16.49.

This authentic sample of 4-chlorofluorenone was readily converted to a 2,4-dinitrophenylhydrazone which melted at 254–255° after recrystallization.

SUMMARY

1. When one mole of the trisulfide produced by the action of dry air on thiobenzophenone was oxidized with chlorine and water, approximately two moles of benzophenone dichloride was formed. When the trisulfide produced by the action of dry air on thiofluorenone was oxidized in this manner, 4,9,9-trichlorofluorene was formed.

2. When one mole of the dibenzophenone trisulfide was reduced with Raney nickel, approximately two moles of diphenylmethane was formed. Likewise the difluorenone trisulfide yielded fluorene.

3. The above reactions prove that the two trisulfides are respectively, 3,3,5,5-tetraphenyldimethylene-1,2,4-trisulfide, and 3,5-bis-diphenylenedimethylene-1,2,4-trisulfide.

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[3] Generously supplied by Dr. R. L. Shriner of this laboratory.

4. Dithiofluorenone yielded fluorene on reduction with Raney nickel, and 4,9,9-trichlorofluorene on oxidation with chlorine and water.

5. 4-Chlorofluorenone was synthesized in an unequivocal manner and characterized by analysis and preparation of its 2,4-dinitrophenylhydrazone.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC AND PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF BUDAPEST]

DIMERIC PROPENYL PHENOL ETHERS. XI. THE FORMATION OF ANTHRAQUINONE DERIVATIVES IN THE CHROMIC ACID DEGRADATION OF DIISOHOMOGENOL (1)

ALEXANDER MÜLLER

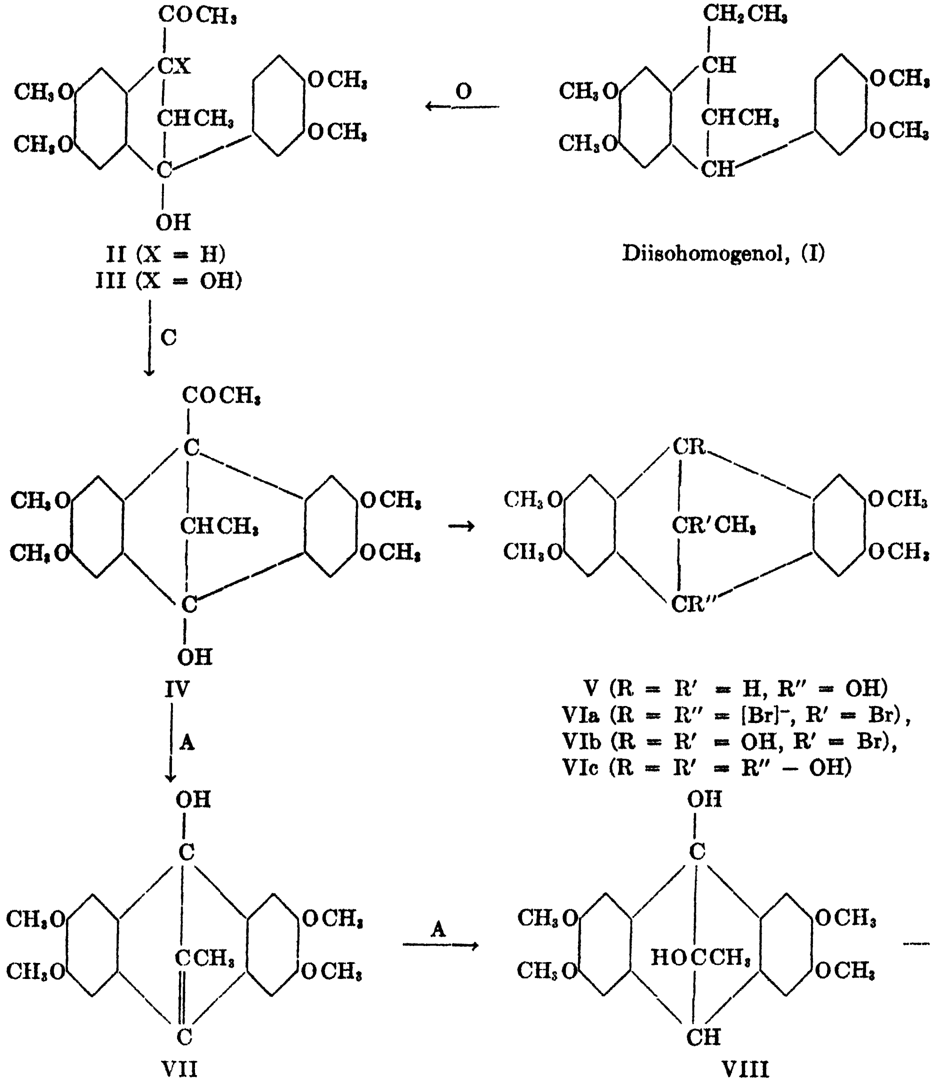
Received June 2, 1947

In view of the identity of diisohomogenol (diisoeugenol 0-dimethyl ether) with 1-veratryl-2-methyl-3-ethyl-5,6-dimethoxyindane (2) (I), the formation of 2,3,6,7-tetramethoxyanthraquinone (XI) in the oxidation of diisohomogenol with chromic acid (3) was made the subject of a detailed investigation. On account of this reaction, Haworth and Mavin rejected the cyclobutane structure originally introduced by Tiemann (4), and strongly advocated by Puxeddu (5), assigning to diisohomogenol a 2,3,6,7-tetramethoxy-9,10-diethyl-9,10-dihydroanthracene formula. Our investigations, beginning in 1942, have shown both structures to be untenable (6). The formation of *o*-veratroylveratric acid in the oxidation of diisohomogenol indicated a phenyltetralin or phenylindane structure, the conversion of hydroxy-keto-diisohomogenol into a phenylnaphthol derivative being first interpreted in favor of the phenyltetralin structure (7). However, continued investigations soon proved that diisohomogenol is actually a phenylindane of the structure (I) (2). On the basis of the established formula, the so-called "red oxidation-product" (XIV) and a diisohomogenol stereomeride were synthesized (1).

Quite recently, Cartwright and Haworth (8), while accepting the phenylindane formula (1), drew attention to the fact that the product of the above mentioned synthesis may not be identical with the diisohomogenol stereomeride, m.p. 106°, obtained by repeated recrystallization from dimerized isohomogenol, the mixture of the two specimens giving a depression in melting point. Repeating earlier determinations of the melting points (1), a mixture of synthetic diisohomogenol, m.p. 105.5–106°, and diisohomogenol, m.p. 106°, from dimerized isohomogenol, was found to melt at 92–95°, while the mixture of the corresponding bromo derivatives, m.p. 125° and 126° respectively, melted at 109–112°. Synthetic diisohomogenol is therefore, quite in agreement with Cartwright and Haworth, not necessarily identical with the stereomerides present in dimerized isohomogenol, four racemic forms of diisohomogenol (cis-cis, cis-trans, trans-cis, trans-trans) being possible. The phenylindane formula (I), however, leaving open the question of the particular spatial arrangement in individual stereomers, remains unaffected by this fact.

In a previous study of the formation of 2,3,6,7-tetramethoxyanthraquinone (XI) from diisohomogenol, evidence was presented (9) that in the oxidation with chromic acid, among other products, 4-pyruvyl-5-veratroylveratrol is formed, this derivative being responsible for the subsequent cyclization (XIII → XI) yielding XI as the final oxidation product. Such a cyclization, however, may occur under appropriate conditions in an earlier step of the degradation, leading to the formation of 9,10-endoethylidene-9,10-dihydroanthracene derivatives.

On oxidizing 1-hydroxy-3′-keto-diisohomogenol (7) (II) in the form of its water-soluble sulfate (10) with no more than two equivalents of chromic acid,


II (X = H)
III (X = OH)

Diisohomogenol, (I)

IV

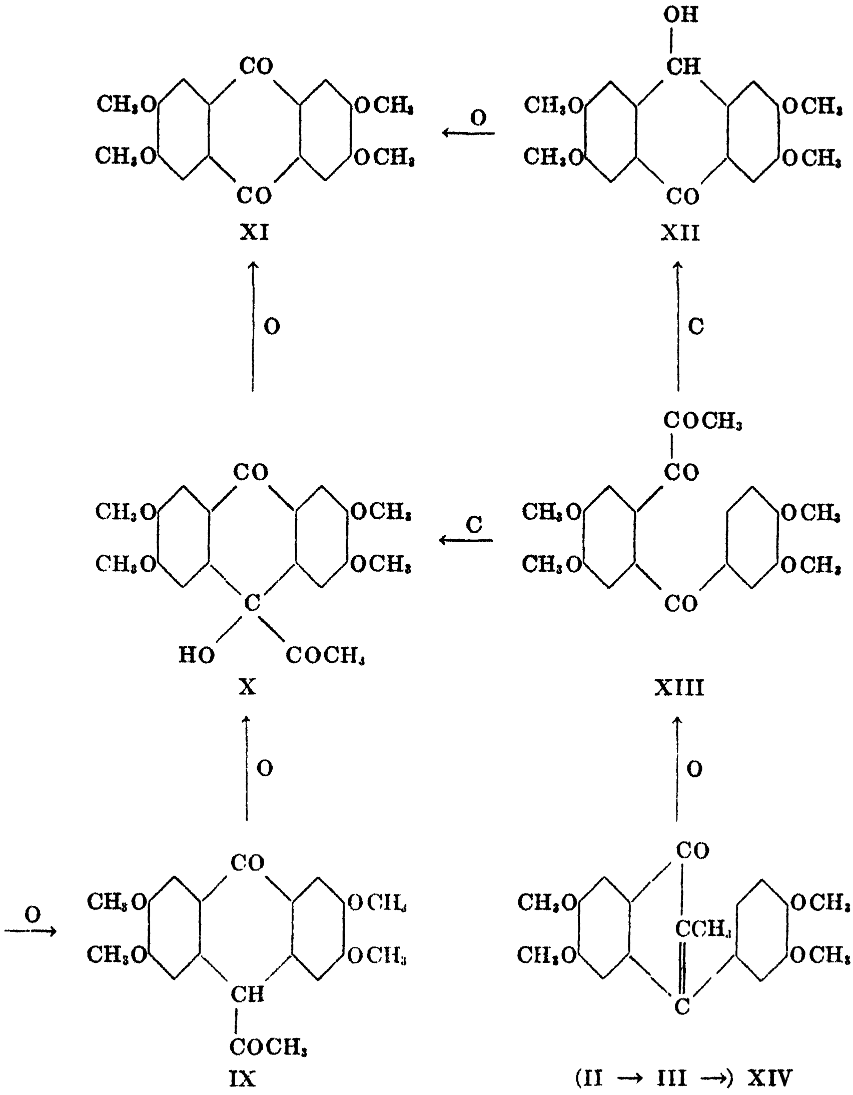
V (R = R′ = H, R″ = OH)
VIa (R = R″ = [Br]⁻, R′ = Br),
VIb (R = R′ = OH, R′ = Br),
VIc (R = R′ = R″ – OH)

VII

VIII

loss of but two atoms of hydrogen takes place, accompanied by simultaneous hydrolysis of the carbenium salt. The resulting product can no longer be converted into *o*-veratroylveratric acid or into veratric acid, while oxidability to 2,3,6,7-tetramethoxyanthraquinone remains preserved. The following reactions characterize this substance as being a 2,3,6,7-tetramethoxy-9-acetyl-9,10-endothylidene-9,10-dihydroanthranol-10 (IV).

(A) The new degradation product forms deeply colored carbenium salts with mineral acids, owing to the anionotropy of the carbon linking the two methoxylated aromatic rings. The salt formation is connected with loss of the acetyl group, the salts (V, R″ = *e.g.* HSO_4^-) yielding the corresponding 9-deacetyl carbinol (V) on hydrolysis.



A = action of alkali
C = condensation
H = hydrolysis
O = oxidation

(B) In alkaline medium the acetyl group is equally unstable, and is readily replaced by a hydroxyl group. At the same time anhydridization seems to take place, prolonged interaction of the alkali resulting in readdition of one mole of water, and giving as the final product a "monobasic" diol (VIII).

(C) The acetyl and hydroxyl groups and the tertiary hydrogen are replaced by bromine to yield a highly unstable bromo-dibromide (VIa). Careful hydrolysis of this salt gave a monobromo-diol (VIb), while more energetic conditions resulted in the formation of a triol (VIc) or of an unsaturated diol.

Following the degradation of IV in the presence of chromic acid, the next step was found to be the oxidative fission of the endo-bridge and the formation of a compound which is regarded as 2,3,6,7-tetramethoxy-9-acetylanthrone (IX), since it forms carbenium salts with loss of the 9-acetyl group, the sulfate yielding on hydrolysis 2,3,6,7-tetramethoxyanthrone. Further oxidation converts IX into 2,3,6,7-tetramethoxy-9-hydroxy-9-acetylanthrone (X), which was actually prepared by oxidizing IX with hydrogen peroxide. This hydroxyanthrone represents the last step before the formation of 2,3,6,7-tetramethoxyanthraquinone (XI), the conversion to the latter taking place with loss of acetaldehyde.

The cyclization of diisohomogenol in a comparatively early step of its oxidation is a reaction quite analogous to the cyclization of 4-pyruvyl-5-veratroylveratrol (XIII) to 2,3,6,7-tetramethoxy-9-hydroxyanthrone (XII) (9) and, presumably, to 2,3,6,7-tetramethoxy-9-hydroxy-9-acetylanthrone (X). It seems to be due to the intermediate formation of a 1,3-dihydroxy-3′-keto-diisohomogenol (III), whose 3-hydroxyl reacts under the influence of the adjacent 3-acetyl with considerable readiness. On the other hand, 1-veratryl-2-methyl-5,6-dimethoxyindenone-3 (XIV) or its hydrate, which possesses no acetyl at carbon 3, does not undergo ring closure under the same conditions, unless oxidative fission of the linkage C^2—C^3 produces such a group.

EXPERIMENTAL

2,3,6,7 - Tetramethoxy - 9 - acetyl - 9,10 - endoethylidene - 9,10 - dihydroanthranol - 10 (IV). Five grams of the carbenium sulfate prepared from 1-hydroxy-3′-keto-diisohomogenol (10) was dissolved in 70 ml. of acetic acid containing 70% of water. The solution was cooled by ice and mixed with 1 g. of chromic acid dissolved in 5.5 ml. of water. An amorphous chromate precipitate was formed which, on heating the mixture on the steam-bath, slowly dissolved. The solution was warmed for another ten minutes. On cooling, a crystalline solid was obtained which was washed thoroughly with water and purified by three recrystallizations from alcohol (or dioxane-water), yielding 1.5 g. of colorless stout prisms, m.p. 196–197°. (From the filtered reaction mixture, 0.5 g. of IX was obtained by extraction with benzene.).

Anal. Calc'd for $C_{22}H_{24}O_6$: C, 68.7; H, 6.3; C—CH_3, 7.8.

Found: C, 68.5, 68.7, 68.7; H, 6.4, 6.6, 6.5; C—CH_3, 7.7.

The substance is readily soluble in chloroform, acetone, ethyl acetate, and dissolves in glacial acetic acid with a yellow color. On oxidation with concentrated nitric acid-glacial acetic acid (3:1), 2,3.6,7 tetramethoxyanthraquinone, m.p. 344° (80% yield), and some V, but no acid degradation product was obtained.

Mineral Acids

2,3,6,7 - Tetramethoxy - 9,10 - endoethylidene - 9,10 - dihydroanthranyl sulfate (V, R'' = HSO₄—) trihydrate. One gram of IV in 10 ml. of glacial acetic acid was mixed with 1 ml. of concentrated sulfuric acid. Orange plates with bright green reflections separated (1.1 g.). The salt, m.p. 178–179°, being sensitive towards moisture, should be kept in a desiccator.

Anal. Calc'd for $C_{20}H_{21}O_4 \cdot HSO_4 + 3H_2O$: C, 50.4; H, 5.9.
Found: C, 51.0, 51.2; H, 5.8, 5.8.

The tetrahydrate was obtained by mixing 1 g. of IV in 10 ml. of glacial acetic acid with no more than 0.5 ml. of concentrated sulfuric acid. Slender prisms of a brighter orange, m.p. 172°, were obtained.

Anal. Calc'd for $C_{20}H_{21}O_4 \cdot HSO_4 + 4H_2O$: C, 48.6; H, 6.1; HSO_4, 19.6.
Found: C, 48.6, 48.8; H, 6.3, 6.4; HSO_4, 20.0.

The chloride was formed by dissolving IV in glacial acetic acid saturated with dry hydrogen chloride or containing acetyl chloride; it consisted of stout needles of deep violet color, which quickly decomposed on exposure to moist air.

2,3,6,7 - Tetramethoxy - 9,10 - endoethylidene - 9,10 - dihydroanthranol - 10 (V). On triturating 5.6 g. of the above sulfate trihydrate with 5 ml. of methyl alcohol at room temperature, a faintly colored powder was obtained. This was dissolved in 30 ml. of dioxane (some XI remaining undissolved) and the filtered solution was mixed with 30 ml. of boiling water giving stout greenish-yellow prisms, m.p. 185°; yield 3.2 g.

Anal. Calc'd for $C_{20}H_{22}O_5$: C, 70.1; H, 6.5; C—CH_3, 4.4.
Found: C, 70.0, 70.1; H, 6.6, 6.6; C—CH_3, 4.3.

Alkali

2,3,6,7 - Tetramethoxy - 9,10 - (10,11- dehydro - endoethylidene) - 9,10 - dihydroanthranol-9 (VII). Five grams of IV in 15 ml. of dioxane was mixed with 15 ml. of a 2 *N* solution of sodium methoxide. A bright yellow solid separated almost immediately. The mixture was kept at room temperature for twelve hours and then diluted with 100 ml. of water. The resulting clear solution soon deposited pale yellow needles when boiled gently. These were recrystallized from *n*-propyl alcohol, m.p. 210–214°; yield 3.0 g.

Anal. Calc'd for $C_{20}H_{20}O_5$: C, 70.6; H, 5.9.
Found: C, 70.2; H, 6.2.

Often, without apparent alteration of the above conditions, a product melting between 215–225° and of composition corresponding to a hemihydrate was obtained. This is probably a mixture of the above and the following compound.

Anal. Calc'd for $C_{20}H_{20}O_5 + 0.5H_2O$. C, 68.7; H, 6.1.
Found: C, 68.6, 68.8; H, 6.1, 6.2.

2,3,6,7 - Tetramethoxy - 9,10 - endo - α - hydroxyethylidene - 9,10 - dihydroanthranol - 9 (VIII). When a solution of 1 g. of IV in 20 ml. of *n*-butyl alcohol containing 1 g. of dissolved sodium was boiled for 30 minutes, yellow needles separated. These were washed with alcohol and recrystallized twice from 30 ml. of acetic acid containing 40% of water. Yellow prisms were obtained, m.p. 226–227°; yield 0.5 g.

Anal. Calc'd for $C_{20}H_{22}O_6$: C, 67.0; H, 6.2.
Found: C, 67.0; H, 6.2.

The carbenium sulfate of this product was obtained by adding 5% of concentrated sulfuric acid to the solution of VIII in glacial acetic acid; deep red needles, m.p. 130–135°.

Bromine

2,3,6,7 - Tetramethoxy - 9,10 - endo - α - bromoethylidene - 9,10 - dihydroanthradibromide (VIa). A solution of 1 g. of IV in 2 ml. of glacial acetic acid was cooled in ice and mixed with 0.5 ml. of pure bromine. The mixture turned into a red-brown mass of crystals, with evolution of hydrogen bromide. The crystals were filtered and washed with about 1 ml. of cold glacial acetic acid as quickly as possible, and then put into a vacuum desiccator without delay, as they are highly sensitive towards moisture and decompose within a few days even if kept in a desiccator. For analysis the salt was dried 2 hours *in vacuo* over phosphorus pentoxide and potassium hydroxide.

Anal. Calc'd for $C_{20}H_{19}BrO_4 \cdot Br_2$: Br, 42.4.
Found: Br, 42.8.

2,3,6,7 - Tetramethoxy - 9,10 - endo - α - bromoethylidene - 9,10 - dihydroanthradiol - 9,10 (VIb). The bromo-dibromide was prepared and isolated as above, and was dissolved in 10 ml. of cold methyl alcohol. The resulting clear solution, on standing at room temperature for two to three days, deposited a colorless crust of crystals. This was recrystallized from ethyl acetate-petroleum ether, yielding 1.0 g. of small prisms, m.p. 150–153° (with decomposition). The substance undergoes slow decomposition in moist air.

Anal. Calc'd for $C_{20}H_{21}BrO_6$: C, 54.9; H, 4.8; Br, 18.3.
Found: C, 54.8, 54.7; H, 5.0, 5.1; Br, 18.4, 18.5.

2,3,6,7 - Tetramethoxy - 9,10 - endo - α - hydroxyethylidene - 9,10 - dihydroanthradiol - 9,10 (VIc). One gram of the foregoing bromo-diol (VIb), refluxed with 50 ml. of alcohol containing 10% of water yields 0.6 g. of stout, colorless prisms, m.p. 143°.

Anal. Calc'd for $C_{20}H_{22}O_7$: C, 64.2; H, 5.9; C—CH_3, 4.0.
Found: C, 64.2, 64.3; H, 6.2, 6.2; C—CH_3, 4.3.

2,3,6,7 - Tetramethoxy - 9,10 - endoethenylidene - 9,10 - dihydroanthradiol - 9,10. One gram of IV was brominated as described above and, without removing the bromo-dibromide (VIa), 0.5 ml. of methyl alcohol was added. The resulting clear brown solution crystallized in a few days, yielding 0.9 g. of small colorless needles containing no bromine. This was recrystallized from ethyl lactate, m.p. 188–189°. The same product was obtained by extracting the bromo-dibromide from the reaction mixture with chloroform and water. The chloroform layer was washed with water and with sodium hydrogen sulfate solution, dried over calcium chloride, and evaporated. The resulting colorless oil crystallized from ether as small prisms (0.2 g.), m.p. and mixed m.p. 188–189°. The substance decolorizes dilute solutions of bromine.

Anal. Calc'd for $C_{20}H_{20}O_6$: C, 67.4; H, 5.7.
Found: C, 67.2, 67.6; H, 5.9, 6.1.

Any of the above products yields XI on oxidation with concentrated nitric acid-glacial acetic acid (3:1) on the steam-bath. The carbinols form deep red solutions in glacial acetic acid containing 5% of concentrated sulfuric acid.

The Degradation of 2,3,6,7-Tetramethoxy-9-acetyl-9,10-endoethylidene-9,10-dihydroanthranol-10 (IV)

2,3,6,7 - Tetramethoxy - 9 - acetylanthrone (IX). (a) A solution of 5 g. of IV in 15 ml. of dioxane was mixed with 5 ml. of 2 *N* sodium methoxide solution. On addition of 2.5 ml. of 30% solution of hydrogen peroxide, the yellow precipitate dissolved with simultaneous decoloration, and crystallization of slender long needles. The crystals were washed with water, and recrystallized from dioxane-water and, subsequently, from xylene; the yield was 2.75 g., m.p. 235°.

(b) The same product was obtained by oxidizing 1-hydroxy-3′-keto-diisohomogenol (II) carbenium salts, but the yields were less satisfactory. A solution of 5 g. of the sulfate prepared from II in 65 ml. of acetic acid containing 75% water was cooled in ice, and a solution of 2 g. of chromic acid in 3 ml. of water was added. On heating the mixture on the steam-bath, the yellow precipitate dissolved. The same temperature was kept for forty minutes after solution was complete. On cooling, faintly colored needles (2.6 g., m.p. about 180°) separated. Simultaneously-formed XIV and XI were removed by recrystallizing this product three times from xylene; pale yellow slender prisms, m.p. 234–235°. The filtered reaction mixture yielded on extraction with benzene 0.3 g. of 5,6-dimethoxy-1-hydroxy-1-veratryl-2-methylindanone.

(c) A solution of 20 g. of II in 100 ml. of glacial acetic acid was mixed with 20 ml. of concentrated nitric acid and kept at room temperature for a week. During this period the mixture was successively diluted with increasing portions of a total of 350 ml. of water. The clear solution was warmed on a steam-bath for sixty minutes, and 0.2 g. of XI was removed by filtration. Water (200 ml.) was added, and the resulting clear solution crystallized on being boiled. The product was recrystallized from alcohol, yielding colorless needles, m.p. 236°; when mixed with specimens prepared according to (a) and (b), 235° and 233–234° respectively; yield 1.4 g.

The product prepared by the above methods should be recrystallized from ethyl alcohol for final purification, in order to remove traces of X, which is particularly disturbing in the subsequent reaction. The samples recrystallized from xylene contain hydrate water which is retained with remarkable persistence.

Anal. Calc'd for $C_{20}H_{20}O_6$: C, 67.5; H, 5.7.
Found: a C, 67.5, 67.8; H, 6.2, 6.2.
b C, 67.7, 67.3; H, 5.9, 5.9.
Calc'd for $C_{20}H_{20}O_6 + 0.5H_2O$: C, 65.7; H, 5.8; C—$CH_3$, 4.1.
Found: c C, 65.8, 65.9, 65.7, 65.9, 66.0; H, 6.0, 5.9, 5.7, 5.8, 6.0; C—CH_3, 4.0.

a = sample recrystallized from ethyl alcohol
b = sample recrystallized from xylene and dried at 13 mm. over phosphorus pentoxide at 140°
c = samples recrystallized from xylene and dried at 100°

The colorless crystals acquire a pale yellow color if exposed to light. The substance is insoluble in aqueous alkalies and readily soluble in chloroform, acetone, or ethyl acetate; the solution in glacial acetic acid is pale yellow. No reaction occurs with hydrazine derivatives, acyl halides, or with dilute solutions of bromine.

On oxidizing 0.6 g. of this substance with 6 ml. of concentrated nitric acid in 12 ml. of glacial acetic acid on the steam-bath for ten minutes, 0.3 g. of XI (golden-yellow needles from diamyl phthalate, m.p. 343°) was formed. On adding water to the filtered reaction mixture, a faintly colored powder was obtained, which crystallized from ethyl acetate-petroleum ether or dioxane-water as colorless long needles, m.p. 205°, insoluble in aqueous alkali, soluble in warm alcoholic alkali with deep green color. This product, probably a *dihydrodi-(4,5-dimethoxysalicylide)*, was not further investigated.

Anal. Calc'd for $C_{18}H_{18}O_8$: C, 59.7; H, 5.0.
Found: C, 59.4, 59.4, 59.6; H, 5.3, 5.4, 5.0.

2,3,6,7-Tetramethoxyanthranyl sulfate. To 1 g. of IX (repeatedly recrystallized from ethyl alcohol) in 100 ml. of glacial acetic acid, 0.5 ml. of concentrated sulfuric acid was added. The carbenium salt crystallized within forty minutes in large cherry-red clusters. The substance, m.p. 175–178°, is extremely sensitive towards moisture.

Anal. Calc'd for $C_{18}H_{17}O_5 \cdot HSO_4 + 0.5H_2SO_4$: SO_4, 31.8.
Found: SO_4, 31.4.

2,3,6,7-Tetramethoxyanthrone. The above carbenium salt (0.6 g.), dissolved in 10 ml. of ethyl alcohol containing 0.2 g. of potassium acetate, gave slender yellow needles, m.p. 175–176°; yield 0.28 g.

Anal. Calc'd for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8.
Found: C, 68.6; H, 5.7.

2,3,6,7-Tetramethoxy-9-hydroxy-9-acetylanthrone (X). A solution of 1 g. of IX in 10 ml. of glacial acetic acid was mixed with 8 ml. of a 10% solution of hydrogen peroxide. The solution, kept at 80° for 30 minutes, deposited small colorless plates, which were recrystallized from ethyl acetate-petroleum ether or dioxane-water. The crystals melt at 325° to a deep cherry-red liquid; yield 0.3 g. The substance is insoluble in aqueous alkali but quickly dissolves on addition of a few drops of alcohol, and is precipitable from the alkaline solution by acetic acid.

Anal. Calc'd for $C_{20}H_{20}O_7$: C, 64.5; H, 5.4.
Found: C, 64.1, 64.3; H, 5.8, 5.8.

Oxidation of this substance in glacial acetic acid with aqueous chromic acid or potassium permanganate, or addition of hydrazine, phenylhydrazine, 3,5-dinitrophenylhydrazine, hydroxylamine, or semicarbazide to its solution in acetic acid, gave in all cases *2,3,6,7-tetramethoxyanthraquinone* (XI) (yellow needles containing no nitrogen, m.p. 343–344°) in fair yield.

Anal. Calc'd for $C_{18}H_{16}O_6$: C, 65.9; H, 4.9.
Found: a C, 65.6; H, 5.0.
b C, 65.8; H, 5.0.
a = sample obtained with hydroxylamine
b = sample obtained with semicarbazide

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SUMMARY

In the oxidation of diisohomogenol (I) with chromic acid, 2,3,6,7-tetramethoxyanthraquinone (XI) arises from 4-pyruvyl-5-veratroylveratrol (XIII) formed in the reaction mixture. Under altered conditions, 1-hydroxy-3′-ketodiisohomogenol (II), also may undergo ring closure by oxidative cyclization; in this case, 9,10-endoethylidene-9,10-dihydroanthracene derivatives are the immediate products. In both cases the acetyl at carbon 3 seems to induce the formation of the anthracene skeleton.

BUDAPEST, HUNGARY

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[Contribution from the Division of Chemistry, Research Department, Ciba Pharmaceutical Products, Inc.]

THE METHOD OF MOLECULAR ROTATION DIFFERENCES APPLIED TO 3-KETO STEROIDS OF THE ALLO SERIES

CARL DJERASSI

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Since the first attempt by Callow and Young (1) on the correlation of optical rotatory power with constitution in the steroid field, a number of papers have appeared, which demonstrated clearly the usefulness of such a tool. Wallis and co-workers (2, 3, 4) and more recently Barton (5–8) have amply reviewed the theoretical grounds on which such work is based, and several investigators (2, 5, 9) have examined the errors inherent in such polarimetric measurements.

During the past few years, incidental to a study of the bromination of 3-keto steroids (10–13), we have measured the rotations of a large number of steroid ketones and related compounds. Since, except for isolated instances, no attempt has been made as yet to correlate the optical properties of these ketones with constitution, such a correlation has been made in this paper. The present work has the advantage that nearly all of the rotations were determined in one laboratory, on the same apparatus, by the same investigator, and under controlled conditions of temperature and concentration. Following the suggestion of Wallis, *et al.*, (2) all measurements were carried out in chloroform.

The data are presented in nine tables and specific literature reference is made only to those rotations which were not measured in our laboratory. In all other cases the rotations given in the tables refer to our measurements, even though some of those rotations have been reported previously.

Wallis and co-workers (2) have examined the contribution of the 3-keto group in four sterols related to cholestane. In Tables I and II are given some additional data on the influence of the 3-keto group in some androstane derivatives. The average value of $\Delta[M]_D = +70$ is in excellent agreement with that obtained by Wallis (2), (+68).

The increase in dextrorotation caused by the introduction of the 4,5 double bond in the saturated ketone II has been noted qualitatively by Callow and Young (1). By subtracting the molecular rotation[1] of the saturated ketone II from that of the unsaturated ketone III, the contribution made by the 4,5 double bond is obtained (Table III). The average increase in molecular rotation due to this factor was 220. If the molecular rotation of the completely saturated steroid I were subtracted from that of the unsaturated ketone III, the "dichromophore Δ value" introduced by Barton (7) would be obtained. Such a calculation is of little use in our case, however, since the rotations of the corresponding hydrocarbons with a 4,5 double bond are unknown except for Δ^4-cholestene and, therefore, the "dichromophore rule" could not be tested.

A practical application of the method of molecular rotation differences is illustrated in considering the effect of the 1,2 double bond[2] (Table IV). The average value of Δ[M]$_D$, the contribution of the 1,2 double bond,of 6 examples was found to be +67. Two Δ^1-3-keto *allo*steroids have been reported in the literature, whose Δ[M]$_D$ values are beyond the experimental error, although a change in solvents may have been involved. Δ^1-Androstene-3,17-dione has been reported to have [α]$_D$ + 148.5° (Δ[M]$_D$ = +125). This high value was very probably due to contamination with the corresponding Δ^4-derivative, since the compound was prepared (14) by collidine dehydrobromination of the 2-bromo derivative, a reaction which in two related instances has been shown (13) to result in the simultaneous formation of the Δ^4-derivative. A repetition of this reaction, described in the experimental section, actually showed this to be the case, and for the pure Δ^1-compound we have found the value for Δ[M]$_D$ to be +64, in good agreement with the other examples. The German investigators (14) also reported the rotation of Δ^1-*allo*pregnene-3,20-dione to be +126° (Δ[M]$_D$ = −6). This negative value can be attributed to contamination with

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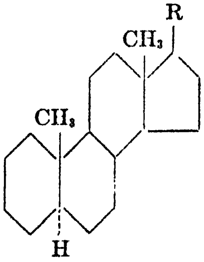
[1] Molecular rotation $[M]_D = \frac{[\alpha]_D \times M.W.}{100}$

TABLE I

STEROIDS UNSUBSTITUTED IN RING A



I

R	[α]$_D$	REF.	[M]$_D$
C_8H_{17}		(2)	92
$OCOC_6H_{11}$[a] (β)[b]	+10		39
$COOCH_3$ (β)[b]	+52	(17, 18)	165
$OCOCH_3$ (β)[b]	+2		6
OH(β)[b]	+8		22
H_2	−0.3		0
=O	+89		244
CH_3 $\lfloor$OH (β)[c]	−17		−49

[a] C_6H_{11} denotes the cyclohexyl radical.

[b] These compounds have all recently been shown (23) to possess the β configuration. It should be noted that in two of our earlier papers (11, 13), the old configuration (α) was still employed.

[c] This refers to the isomer derived from active 17-methyltestosterone.

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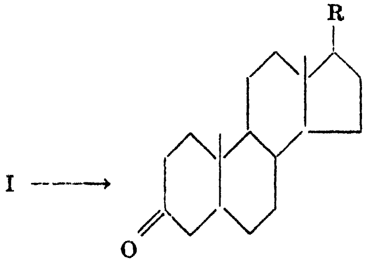
[2] The two examples of this type discussed by Callow and Young (1), were actually *hetero*-Δ^1-ketones [*cf.* Butenandt and Rubenstroth-Bauer, *Ber.*, **77**, 397 (1944)].

the corresponding Δ^{16}-derivative, which has been reported (15) to have a lower rotation than the parent ketone, and which could easily have been present as an impurity, particularly since the product was not chromatographed. Another possibility may have been that the rotation of the saturated ketone was measured in ethanol and that of the unsaturated derivative in chloroform.

A further illustration of the usefulness of this method is given in Table V, in which is considered the influence of a bromine atom in position 2. As can be seen, the $\Delta[M]_D$ values of the seven examples differ widely and no apparent correlation seems possible. It is evident that in introducing a bromine atom into the 2-position of a 3-keto steroid II, two diastereoisomers are possible, although as yet only one isomer has been isolated in all the instances described in the literature. Indirect evidence for the presence of two diastereoisomers in the introduction of a bromine in the 4-position of 3-keto steroids of the *normal* series has been presented frequently (*cf.* 16), since in that case only one diastereoisomer can be dehydrobrominated with ease. Such evidence is not available for 2-bromo-3-keto *allo*steroids V, since *trans* elimination of hydrogen bromide is possible with both diastereoisomers. The data presented in Table V point towards the presence of both isomers. Four of the examples showed $\Delta[M]_D$ values of *ca.* +30° and two compounds exhibited $\Delta[M]_D$ values around +92°. 2-Bromoandrostan-17β-ol-3-one 17-acetate had an intermediate value, which

TABLE II

INFLUENCE OF 3-KETO GROUP



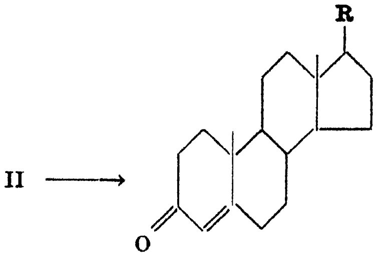
II

R	$[\alpha]_D^a$	$[M]_D^a$	$\Delta[M]_D^a$ II−I
C_8H_{17}	41	158	66
$OCOC_6H_{11}$	27	108	69
$COOCH_3$	72	239	74
$OCOCH_3$	26	86	80
OH	30	87	65
H_2	27	74	74
=O	105	302	58
CH_3 OH	7	21	70

[a] All values in Tables II to VI are positive and are not marked by (+) signs.

TABLE III

Influence of 4,5 Double Bond



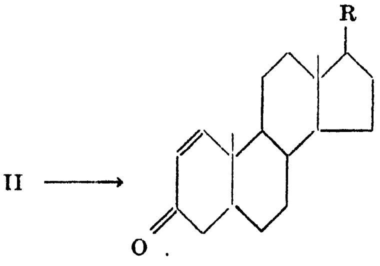
III

R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ III−II
C_8H_{17}	93	357	199
$OCOC_6H_{11}$	83	330	222
$COOCH_3$	145	479	240
$OCOCH_3$	91	300	214
OH	109	314	227
H_2	101	275	201
=O	187	535	233
CH_3 $\lfloor$OH[a]	80	242	221

[a] 17-Methyltestosterone.

TABLE IV

Influence of 1,2 Double Bond

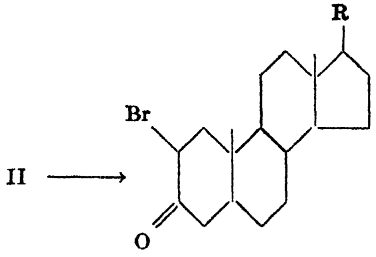


IV

R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ IV−II
C_8H_{17}	58	223	65
$OCOC_6H_{11}$	45	178	70
$COOCH_3$	93	307	68
$OCOCH_3$	47	155	69
OH	52	150	63
=O	128	366	64

TABLE V

INFLUENCE OF BROMINE IN 2-POSITION

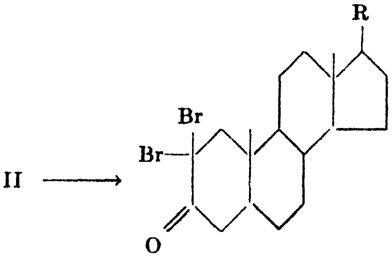


V

R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ V−II
C_8H_{17}	40	186	28
$OCOC_6H_{11}$	43	206	98
$COOCH_3$	79	325	86
$OCOCH_3$	35	144	58
OH	33	122	35
H_2	29	102	28
=O	90	330	28

TABLE VI

INFLUENCE OF BROMINES IN 2,2-POSITION



VI

R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ VI−II
C_8H_{17}	111[a]	604	446
$OCOC_6H_{11}$	110	614	506
$COOCH_3$	136	666	427
$OCOCH_3$	111[b]	544	458

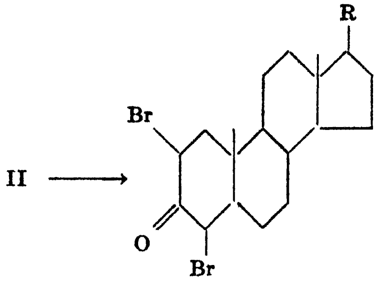
[a] The rotation of the analytical sample (12) was +104°, but it has been possible to demonstrate (13) by a polarimetric method that the highest rotation of this compound should be +111°.

[b] The analytical sample (13) had $[\alpha]_D$ +106° (*cf.* Footnote *a*).

might indicate that the compound is an approximately 1:1 mixture of the two diastereoisomers. Tentatively, we assign the α-notation to the more dextrorotatory compounds and the β-notation to the lower rotating ones.

TABLE VII

Influence of Bromines in 2,4-Position

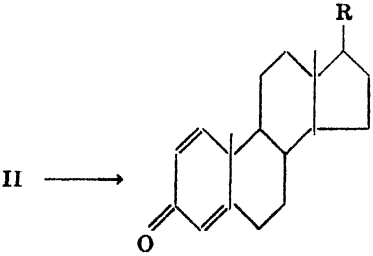


VII

R	$[\alpha]_D$	$[M]_D$	$\Delta[M]_D$ VII−II
C_8H_{17}	+3	+16	−142
$OCOC_6H_{11}$	−6	−33	−141
$COOCH_3$	+24	+118	−121
$OCOCH_3$	−11	−54	−140

TABLE VIII

Influence of 1,2 and 4,5 Double Bonds



VIII

R	$[\alpha]_D$	REF.	$[M]_D$	$\Delta[M]_D$ VIII−II
C_8H_{17}	31		+118	−40
$OCOC_6H_{11}$	45		+178	+70
$COOCH_3$	82		+269	+30
$OCOCH_3$	28	(19)	+92	+6
OH	20		+57	−30
=O	116	(19)	+329	+27

Additional evidence for the presence of two diastereoisomeric 2-bromo ketones V is presented in Tables VI and VII, which contain data relating to substitution of two bromine atoms in the 2,2 and 2,4 positions respectively. In both instances, the agreement of the $\Delta[M]_D$ values is within the experimental error.

Such agreement is to be expected, since in 2,2-dibromo ketones VI only one isomer is possible and since it has been shown (13) that the 2,4-isomers VII, even when prepared directly, always are formed by rearrangement of the intermediate 2,2-dibromo compounds. Thus, although in the case of the 2,4-dibromo derivatives diastereoisomerism is possible, it is quite conceivable that always only one and the same isomer is formed predominantly in the four series examined.

The simultaneous introduction of a 1,2 and 4,5 double bond (Table VIII) seems to result in vicinal effects (20, 21), which preclude any correlation of polarimetric data.

Table IX contains a summary of the average $\Delta[M]_D$ values and the deviations from the arithmetic mean. The agreement is in general within 10% except in the case of the $\Delta^{1,2} + \Delta^{4,5}$ double bond.

TABLE IX

SUMMARY

CONTRIBUTION OF:	AV. $\Delta[M]_D$[a]	NO OF EXAMPLES	RANGE OF DEVIATION FROM ARITHMETIC MEAN[a]	
3-Ketone	+70	8	−12	+10
$\Delta^{4,5}$ double bond	+220	8	−21	+20
$\Delta^{1,2}$ double bond	+67	6	−4	+3
2-Br	(+52)	7	(−24)	(+46)
α	+92	2	−6	+6
β	+30	4	−2	+5
2,2,-Br	+459	4	−32	+47
2,4-Br	−136	4	−6	+15
$\Delta^{1,2} + \Delta^{4,5}$ double bond	(+11)	6	(−51)	(+59)

[a] The figures given in parentheses are not significant.

EXPERIMENTAL

All rotations were determined on 5–10 mg. of sample in 1.2 cc. of chloroform in a 1 dcm. tube of 1 cc. capacity at 23–24°, using the sodium D line.

Androstan-17β-ol-17 hexahydrobenzoate. Androstan-17β-ol was refluxed for four hours with hexahydrobenzoyl chloride (22) and pyridine, the solution diluted with water, and the product was recrystallized from ethanol to constant rotation and melting point; m.p. 112.5–113°, $[\alpha]_D^{24}$ +9.7°.

Anal. Calc'd for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95.

Found: C, 81.18; H, 11.11.

2-Bromoandrostane-3-one. Androstane-3-one was brominated in C.P. glacial acetic acid and the product which crystallized out was filtered and recrystallized from ethanol; m.p. 210.5–211.5° (dec.), $[\alpha]_D^{23}$ +29.3°.

Anal. Calc'd for $C_{19}H_{29}BrO$: C, 64.58; H, 8.27; Br, 22.62.

Found: C, 64.15; H, 8.35; Br, 22.65.

Dehydrobromination of 2-bromoandrostan-3,17-dione. A solution of 1.5 g. of 2-bromoandrostan-3,17-dione in 6 cc. of γ-collidine was refluxed for one hour and the reaction mixture was worked up by chromatography and spectrophotometric analysis of the chromatogram fractions as described earlier for similar cases (13); there was thus obtained 0.14 g. (12%) of crude Δ^4-androstene-3,17-dione (max. at 242.5 mμ log E = 4.09, $[\alpha]_D^{23}$ +175.4°) and

0.42 g. (36%) of the Δ^1-isomer ($[\alpha]_D^{24}$ +129.6°). After recrystallization from hexane, Δ^1-androstene-3,17-dione was obtained as rosettes of needles, m.p. 140–142°, $[\alpha]_D^{24}$ +127.5°, max. at 230 mμ log E = 4.01 (ethanol); Butenandt and co-workers (14) reported m.p. 138–139°, $[\alpha]_D^{23}$ +148.5° (solvent unspecified) for the Δ^1-isomer which was obtained on direct crystallization rather than purified by chromatographing.

Anal. Calc'd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15.
Found: C, 80.11; H, 9.41.

The author is indebted to Dr. A. F. St. André for furnishing some of the androstane derivatives shown in Table I and to Miss Helen Dudek for assistance in the polarimetric determinations. It is a pleasure to acknowledge the interest of Prof. A. L. Wilds of the University of Wisconsin.

SUMMARY

The method of molecular rotation differences has been applied to a number of steroid ketones of the *allo* configuration and it has been shown that definite values can be assigned to the contribution of the following substituents on the molecular rotation of the compound: 3-ketone, 1,2 double bond, 4,5 double bond, 2,2-dibromide, 2,4-dibromide. Evidence is presented for diastereoisomerism in the 2-bromo-3-keto steroids of the *allo* series.

Summit, New Jersey

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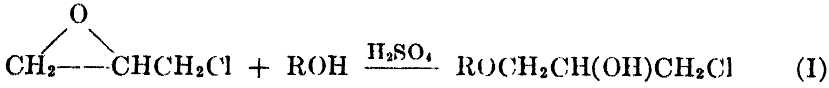
[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES OF THE UNIVERSITY OF FLORIDA]

EPOXY ETHERS AND ETHER AMINO ALCOHOLS[1]

H. FLORES-GALLARDO AND C. B. POLLARD

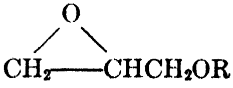
Received June 26, 1947

The condensation of epoxyalkanes with alcohols in the presence of sulfuric acid was reported by Fourneau and Ribas (1) and Kharasch and Nudenberg (2). A similar method was used in this laboratory for the condensation of ten aliphatic alcohols (methanol, ethanol, propanol-1, propanol-2, butanol-1, 2-methylpropanol-1, pentanol-1, 2-methylbutanol-1, 3-methylbutanol-1, and hexanol-1) with 1,2-epoxy-3-chloro propane.

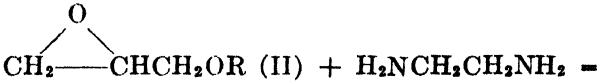


$$\overset{\quad O}{CH_2\text{——}}CHCH_2Cl + ROH \xrightarrow{H_2SO_4} ROCH_2CH(OH)CH_2Cl \qquad (I)$$

The 1-alkoxy-2-hydroxy-3-chloropropanes (I) obtained were used to synthesize a number of new compounds.

The synthesis of epoxy ethers by the reaction of (I) with NaOH was investigated by Reboul (3), Henry (4), Nef (5), Lespieau (6), Fourneau and Samdahl (7), and Fairbourne, Gibson, and Stephens (8). By suitable modifications, the method was here extended to produce compounds of the type  $\overset{\quad O}{CH_2\text{——}}CHCH_2OR$ (II) where R was methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *n*-pentyl, 2-methyl-*n*-butyl, 3-methyl-*n*-butyl, and *n*-hexyl. The atomic refractions of the constituents (not including the epoxy oxygen) of these epoxy ethers (II) were added and then subtracted from their observed molar refractions. The difference was the refractive equivalent of epoxy oxygen, *i.e.*, 1.890. These data are given in Table II.

Ten new ether amino alcohols of the type $H_2NCH_2CH_2NHCH_2CH(OH)$-CH_2OR were obtained by the monoalkylation of (II) with ethylene diamine.



$$\overset{\quad O}{CH_2\text{——}}CHCH_2OR\ (II) + H_2NCH_2CH_2NH_2 = H_2NCH_2CH_2NHCH_2CH(OH)CH_2OR$$

EXPERIMENTAL

Synthesis of 1-methoxy-2-hydroxy-3-chloropropane. In a 2-l., two-necked, round bottomed flask, fitted with a stirrer and a reflux condenser were placed nine moles (365 cc.) of methanol and 6.7 cc. of H_2SO_4 (*d.* 1.84). Three moles (235 cc.) of 1,2-epoxy-3-chloropropane was added dropwise through the top of the reflux condenser from a dropping-funnel. The mixture was stirred and refluxed for six hours. An excess of $BaCO_3$ (30 g.) was added and stirred at room temperature for several hours. The filtrate was distilled

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[1] This paper is abstracted from a portion of a dissertation submitted by H. Flores-Gallardo to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy, July, 1947.

TABLE I

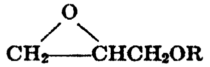
Data Concerning Chloro-Hydroxy-Ethers of the Type $ROCH_2CH(OH)CH_2Cl$

R	Molar ratio of alcohol to 1,2-epoxy-3-chloropropane	Yield percent	B.p. at 20 mm., °C.	d^{25}_4	n^{25}_D	Molar refraction	
						Obs.	Calc'd.
Methyl	3 to 1	68.3	76.5	1.1570	1.4422	28.49	28.70
Ethyl	2 to 1	60.0	80–82	1.0914	1.4370	33.30	33.32
n-Propyl	2 to 1	51.0	97–98	1.0526	1.4378	38.11	37.94
Isopropyl	3 to 1	28.2	87–87.5	1.0530	1.4370	37.96	37.94
n-Butyl	2 to 1	57	110–111	1.0444	1.4420	42.22	42.56
Isobutyl	3 to 1	37.6	100.0–100.2	1.0313	1.4386	42.46	42.56
n-Pentyl	2 to 1	52	120	1.0216	1.4441	46.98	47.17
3-Methyl-*n*-butyl	2 to 1	44.4	118–119	1.0223	1.4436	46.90	47.17
2-Methyl-*n*-butyl[a]	2.3 to 1	45.3	114.8–115.5	1.0638	1.4492	45.56	47.17
n-Hexyl	3 to 1	41.6	133	1.0026	1.4450	51.67	51.79

[a] This compound showed 22.19% Cl on analysis compared to a theoretical of 19.62%. The slight decomposition of the compound on distillation is a possible explanation of the high chlorine value obtained and the low observed molar refraction.

TABLE II

Data Concerning Epoxy Ethers of the Type



$CH_2\overset{O}{\text{———}}CHCH_2OR$

R	Yield, percent	B.p. °C.	d^{25}_4	n^{25}_D	Molar refr. obs.	Molar refr., calc'd (not incl. epoxy oxygen)	Refractive equivalent of epoxy oxygen
Methyl	68	53.5–53.7 at 85 mm.	0.9798	1.4012	21.859	20.115	1.744
Ethyl	75	61.0 at 65 mm.	0.9430	1.4046	26.544	24.733	1.811
n-Propyl	60.2	77.7 at 65 mm.	0.9203	1.4103	31.284	29.351	1.933
Isopropyl	66.6	68.0 at 65 mm.	0.9139	1.4068	31.272	29.351	1.921
n-Butyl	87.5	69.7 at 20 mm.	0.9087	1.4150	35.873	33.969	1.904
Isobutyl	75.2	65.5 at 20 mm.	0.8998	1.4112	35.936	33.969	1.967
n-Pentyl	74.9	86.5–86.7 at 20 mm.	0.9015	1.4201	40.484	38.587	1.897
3-Methyl-*n*-butyl	80.4	80.7 at 20 mm.	0.8982	1.4185	40.501	38.587	1.914
2-Methyl-*n*-butyl	64.4	78.0–78.5 at 20 mm.	0.8997	1.4186	40.443	38.587	1.856
n-Hexyl	86.5	105.0 at 20 mm.	0.8943	1.4242	45.167	43.205	1.962

The atomic refraction of epoxy oxygen given in Table II averages 1.890

TABLE III

Data Concerning Ether Amino Alcohols of the Type $H_2NCH_2CH_2NHCH_2CH(OH)CH_2OR$

R	Yield percent	B.p °C	d^{25}_4	n^{25}_D	Molar refraction		Nitrogen percent	
					Found	Calc'd	Found	Calc'd
Methyl	82.9	117–119 at 2 mm.	1.0446	1.4748	39.93	40.09	18.77	18.90
Ethyl	78.6	128 at 3 mm.	1.0265	1.4740	44.41	44.71	17.23	17.27
n-Propyl	72.5	130–131 at 2 mm.	0.9987	1.4683	49.08	49.33	15.84	15.89
Isopropyl	76.6	126 at 3 mm.	0.9875	1.4650	49.34	49.33	15.88	15.89
n-Butyl	80.5	134–135 at 2 mm.	0.9775	1.4654	53.85	53.95	14.62	14.72
Isobutyl	76.3	133 at 3 mm.	0.9694	1.4627	53.99	53.95	14.66	14.72
n-Pentyl	83.2	149–150 at 2 mm.	0.9660	1.4645	58.41	58.56	13.65	13.71
3-Methyl-*n*-butyl	84.0	145.7 at 2 mm.	0.9635	1.4641	58.52	58.56	13.66	13.71
2-Methyl-*n*-butyl	77.2	143.7 at 3 mm.	0.9630	1.4648	58.61	58.56	13.56	13.71
n-Hexyl	78 7	158 at 2 mm.	0.9549	1.4650	63.19	63.18	12.74	12.85

first at atmospheric pressure to remove the excess methanol and then at 20 mm.; 1-methoxy-2-hydroxy-3-chloropropane was collected at 76.5°.

In Table I are shown the results obtained when this synthesis was extended to include other alcohols.

Synthesis of 1,2-epoxy-3-methoxypropane. In a 3-l., three-necked, round bottomed flask, provided with an efficient mechanical stirrer and a reflux condenser were placed two liters of ether and two moles (216 cc.) of 1-methoxy-2-hydroxy-3-chloropropane. The flask was surrounded by an ice-water bath, and three moles (120 g.) of finely powdered sodium hydroxide was added in small portions with vigorous stirring. The water-bath was allowed to reach room temperature and the mixture was stirred for eight hours. Then 500 cc. of water was added and the layers formed were separated. The aqueous layer was extracted with ether, the combined ether solutions distilled, and 1,2-epoxy-3-methoxypropane collected at 53.5–53.7° at 85 mm.

The results obtained, when this procedure was used to synthesize other epoxy ethers, are summarized in Table II.

Synthesis of N-(2-hydroxy-3-methoxy propyl)ethylene diamine. To 10 moles of boiling ethylene diamine hydrate contained in a 2-l., three-necked, round bottomed flask, provided with a reflux condenser and a mechanical stirrer, was added dropwise through the top of the condenser one mole (90 cc.) of 1,2-epoxy-3-methoxypropane. The mixture was stirred and refluxed for five hours. It was then distilled and the desired product was collected at 117–119° at 2 mm.

This procedure was followed in the syntheses of other ether amino alcohols; these data are given in Table III.

GAINESVILLE, FLA.

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[Contribution from the Division of Physiology, National Institute of Health, and the Chemical Laboratory of the University of California]

THE MANNICH REACTION WITH DIHYDROCODEINONE

HENRY RAPOPORT[1] AND LYNDON SMALL

Received June 27, 1947

The outstanding pharmacological advantages (1) of methyldihydromorphinone (Metopon) (2) over other drugs in the morphine series has stimulated interest in a more practical synthesis of this compound and in nuclear substituted morphine derivatives generally (3). As a promising method for possibly accomplishing both these objectives, the Mannich reaction with dihydro ketones in the codeine series was selected for investigation. If the reaction proceeded normally, dialkylaminomethyl ketones, a new type of morphine derivative, should result, and these might then be converted to the methyl ketones.

When dihydrocodeinone (I) was subjected to the Mannich reaction with dimethylamine hydrochloride and formaldehyde according to the modification of Fry (4), reaction took place as evidenced by the inability to recover any starting material; the crystalline product (about 40% yield) seemed to be a mixture, which could apparently be separated by laborious fractionation from methanol into a low-melting (174°) and a high-melting (247°) portion. These are shown below to be dimorphic forms of the same base.

If condensation had taken place at the reactive 1-position as well as with the expected α-hydrogen in the 7-position, the resulting complexity of the reaction product might explain its resistance to purification. Hence, the reaction was next studied with a compound in which the 1-position was blocked.

From 1-bromodihydrocodeinone (II) (5), dimethylamine hydrochloride, and formaldehyde, a crystalline product was isolated in 90% yield. However, this was not the expected dimethylaminomethyl ketone, since the substitution of diethylamine for dimethylamine gave the same product. The failure of this compound to sublime indicated it might be dimolecular, and analysis and molecular weight determinations strongly supported the assignment of a methylenebis-(1-bromodihydrocodeinone) structure. Juncture through the aromatic ring was made improbable by the recovery of dihydrodesoxycodeine-D (V) (6) unchanged under the conditions of the reaction, and therefore 7,7′-methylenebis-(1-bromodihydrocodeinone)[2] (III) was designated as the structure of the reaction product.

The formation in high yield of a methylenebis compound by the above reaction instead of the expected Mannich base was investigated further by replacing the dimethylamine with trimethylamine. No reaction took place in the presence of the tertiary amine, indicating that the complex formation between amine and formaldehyde, which occurred with the secondary amine but not with the tertiary, was a necessary condition for reaction.

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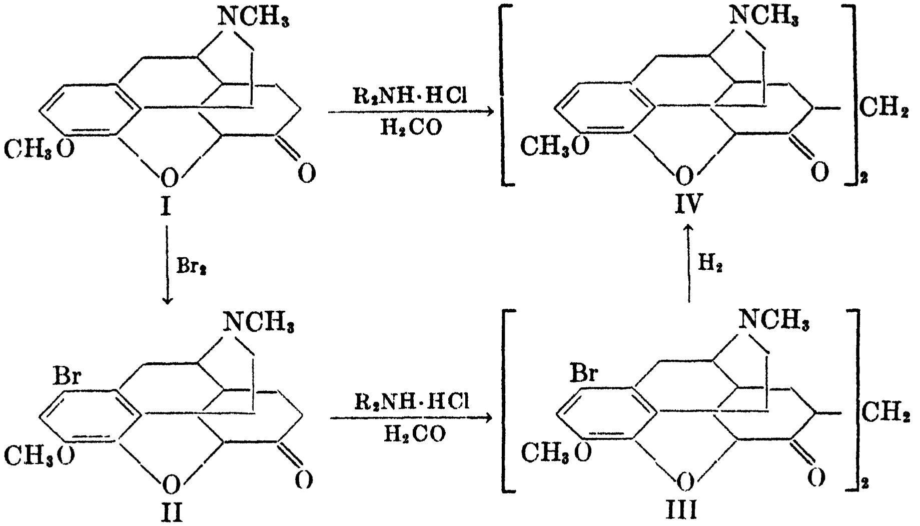
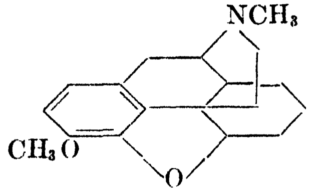
[2] That the structure might be 5,5′- or 5,7′- is recognized, but the 7,7′-linkage was selected as being the most probable because of its much less hindered nature.

Debromination of (III) by catalytic hydrogenation using a palladous chloride-gum arabic catalyst (5) proceeded slowly to give a 76% yield of the des-bromo compound, 7,7′-methylenebisdihydrocodeinone. This des-bromo compound should be identical with the reaction product from dihydrocodeinone, since the unreactivity of dihydrodesoxycodeine-D seems to eliminate the 1-position as a possible site of reaction.





V

Hence, the condensation with dihydrocodeinone was re-examined, and by using the des-bromo compound prepared by hydrogenolysis as seed, a 55% yield of 7,7′-methylenebisdihydrocodeinone (IV) was obtained. It crystallized in dimorphic forms, m.p. 174–175° and 247–248°, either of which was obtainable directly from acetone solution. The high-melting form could also be obtained by slowly heating the low-melting form above its melting point or by heating it at 150° in a vacuum. Both forms and the compound prepared by reductive debromination of the bromo analog were identical as shown by specific rotations and mixed melting points.

The methylenebis structure of (IV) was further substantiated by analysis, molecular weight determinations, and formation of a monosemicarbazone. A dihydrochloride and dimethiodide were prepared, and reaction took place with hydroxylamine but the oxime could not be isolated pure. Attempted demethylation to the morphine analog gave only resinous products.

Thus a new type of morphine derivative has been synthesized which may be considered as an analog of methyldihydrocodeinone. Other dimolecular morphine derivatives are known, but they result from either dimolecular oxidation (7) or reduction (8), and nothing is known of the structure of the reported dicodeylmethane (9).

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes; rotations are in 95% alcohol unless otherwise specified. Microanalyses were performed by C. W. Koch of the Department of Chemistry, University of California.

7,7′-Methylenebis-(1-bromodihydrocodeinone) (*III*). A mixture of 1.8 g. (0.06 mole) of paraformaldehyde, 4.8 g. (0.059 mole) of dimethylamine hydrochloride, 25 ml. of benzene, 15 ml. of nitrobenzene, and 0.05 ml. of concentrated hydrochloric acid was placed in a two-necked flask fitted with a mechanical stirrer and reflux condenser (protected from moisture with a calcium chloride tube). After stirring and refluxing (bath temp. 110°) for 30 min. during which most of the paraformaldehyde went into solution, the sublimed paraformaldehyde was scraped from the condenser (in the shorter neck of the flask) back into the reaction mixture, and 20 g. (0.053 mole) of 1-bromodihydrocodeinone (II) (1) was added. Stirring and refluxing (bath temp. 120–125°) were continued for 1.5 hours with a water-trap present during the last hour (total water collected, 0.8 ml.), and then the solution was poured into 250 ml. of 2% acetic acid. The organic layer was separated, extracted with two 50-ml. portions of 2% acetic acid, and the combined aqueous extracts, after washing with ether, were basified with concentrated ammonia and extracted thoroughly with four 100-ml. portions of ethyl acetate. The residue after evaporation under reduced pressure of the combined, dried ethyl acetate extracts was digested with 250 ml. of ethanol and on cooling gave 11.7 g. of crystals, m.p. 244–250°. Concentration of the mother liquor to 75 ml. yielded another 4.6 g., m.p. 240–250°, and an additional 2.1 g. of material, m.p. 215–225°, was obtained by further concentration to 50 ml.; total, 18.4 g. of crude, 90%. It is insoluble in ether and methanol, slightly soluble in ethanol and acetone, and very easily soluble in dioxane and benzene. It does not sublime up to 200°/0.05 mm. and was best purified by dissolving in excess acetone, concentrating the solution until crystals appeared, and then cooling. In this way, 75% of the crude product was obtained as material melting from 272–274°. Repeated crystallization from acetone raised the m.p. to 274–275°, $[\alpha]_D^{20}$ −287° (dioxane, $c = 0.90$).

Anal. Calc'd for $C_{37}H_{40}Br_2N_2O_6$: C, 57.82; H, 5.25; N, 3.65; M.W., 768.

Found: C, 57.90; H, 5.37; N, 3.54; M.W., 747 (cryoscopic in benzene).

The *dihydrochloride* was prepared with 0.75 *N* hydrochloric acid from which it also was recrystallized. It is extremely soluble in water and abs. ethanol, and final purification was accomplished by washing the crystals with a small amount of cold abs. ethanol followed by a mixture of abs. ethanol-ether (1:1) and then abs. ether. The thoroughly dried material was very hygroscopic and absorbed three moles of water when exposed to the atmosphere; the hydrate had m.p. 271-273°, $[\alpha]_D^{20}$ −243° (alcohol, $c = 1.07$).

Anal. Calc'd for $C_{37}H_{42}Br_2Cl_2N_2O_6 + 3H_2O$: C, 49.62; H, 5.40; H_2O, 6.04.

Found: C, 49.94; H, 5.26; H_2O, 6.67.

When 1-bromodihydrocodeinone hydrochloride was substituted for the free base in the above condensation, it was necessary to double the total volume of solvent and increase the nitrobenzene-benzene ratio to 1:1 in order to maintain stirring, as a gummy solid separated toward the end of the reaction. All the other conditions were kept the same, and a 61% yield of 7,7′-methylenebis-(1-bromodihydrocodeinone) resulted.

The same methylenebis compound was obtained in 48% yield when diethylamine hydrochloride was substituted for dimethylamine hydrochloride in the above reaction with 1-bromodihydrocodeinone. However, when trimethylamine hydrochloride was used, no reaction appeared to occur. The paraformaldehyde remained completely undissolved after the initial 30-min. reflux period, and sublimation at 150°/0.3 mm. of the residue after evaporation of the ethyl acetate gave 81% of unchanged starting material as crystalline sublimate. From the small amount of slightly brown residue no 7,7′-methylenebis-(1-bromodihydrocodeinone) could be isolated.

Attempted condensation with dihydrodesoxycodeine-D (V). Using the procedure given above, a condensation was carried out with 3.0 g. (0.0105 mole) of dihydrodesoxycodeine-D (6). The residue after evaporation of the ethyl acetate was sublimed at 95°/0.2 mm. and 2.7 g., 90%, of the starting material was recovered as crystalline sublimate, m.p. 104–106°.

Hydrogenolysis of 7,7′-methylenebis-(1-bromodihydrocodeinone). Hydrogenolysis of 1.0 g. (0.0013 mole) of 7,7′-methylenebis-(1-bromodihydrocodeinone) in 25 ml. of 2 *N* acetic acid with 1.5 g. of sodium acetate, 1 ml. of 1% gum arabic solution, and 3 ml. of a 1% palladous chloride solution proceeded slowly and ceased completely after fifteen hours, with the absorption of 2.3 moles of hydrogen. The solution was warmed on the steam-bath for 10 min. after the addition of decolorizing carbon and 25 ml. of water, and filtration gave a clear filtrate which was basified with concentrated ammonia. The resulting precipitate, after copious washing, was free of halogen as evidenced by a negative Beilstein test, and crystallization from acetone gave 0.6 g. (76%) of the des-bromo compound, 7,7′-methylenebisdihydrocodeinone (IV). It melted from 169–174° and on slow, continued heating above its melting point completely resolidified by 200° and melted sharply at 246–247°, $[\alpha]_{\mathrm{D}}^{20}$ −322° (dioxane, c = 0.94). Conversion to the high-melting form could also be accomplished by heating at 150° for 10 hours in a vacuum.

7,7′-Methylenebisdihydrocodeinone (IV). The condensation was carried out as described above for the bromo analog, using 2.8 g. (0.092 mole) of paraformaldehyde, 7.5 g. (0.092 mole) of dimethylamine hydrochloride, 0.05 ml. of concentrated hydrochloric acid, 50 ml. of benzene, 25 ml. of nitrobenzene, and 25 g. (0.084 mole) of dihydrocodeinone (I); 1.6 ml. of water was collected. The residue after evaporation of the ethyl acetate was dissolved in 75 ml. of acetone and seeded with the crystals obtained by hydrogenolysis of the bromo analog. Cooling gave 10 g. of crystalline material, m.p. 165–168°, and concentration of the mother liquor to 25 ml. resulted in an additional 4 g., m.p. 160–165°, total, 14 g., 55%. Seeding with either the low-melting form or the high-melting form of the des-bromo compound gave crystals of only the low-melting form. By heating the low-melting form at 150° for 10 hours in a vacuum or by concentrating the acetone solution until considerable solid had separated and then cooling slowly, the high-melting form, m.p. 247–248°, could be obtained. A pure sample of the low-melting form was prepared by several crystallizations from acetone and melted at 174–175°. It showed no loss in weight when heated at 150° in a vacuum, had $[\alpha]_{\mathrm{D}}^{20}$ −314° (dioxane, c = 0.943), and did not depress the m.p. of material melting at 247–248°. Pure high-melting crystals were obtained by several crystallizations from acetone as described above, m.p. 247–248°, $[\alpha]_{\mathrm{D}}^{20}$ −318° (dioxane, c = 1.064); admixture with material from the hydrogenolysis of the bromo analog caused no depression in m.p. It does not sublime up to 250°/0.1 mm

Anal. Calc'd for $C_{37}H_{42}N_2O_6$: C, 72.76; H, 6.93; N, 4.59; M.W., 610; Neut. Equiv., 305.
Found: C, 72.99; H, 6.76; N, 4.67; M.W., 581 (cryoscopic in benzene); Neut. Equiv., 314.

The *dihydrochloride*, prepared with 3 *N* hydrochloric acid, was recrystallized from 1 *N* hydrochloric acid, and excess acid was removed by washing with a small portion of cold abs. ethanol, a mixture of abs. ethanol-ether (1:1), and then repeated with abs. ether. After drying in a vacuum at 100° it melted at 278–280° with decomp. and on exposure to air avidly absorbed 5 moles of water; the hydrate had $[\alpha]_{\mathrm{D}}^{20}$ −252° (alcohol, c = 0.96).

Anal. Calc'd for $C_{37}H_{44}Cl_2N_2O_6 + 5H_2O$: C, 57.43; H, 7.03.
Found: C, 57.46; H, 6.91.

The *dimethiodide* was prepared in and purified from methanol. After thorough drying, it absorbed 2 moles of water on exposure to the air, m.p. 270–272° with decomp., $[\alpha]_D^{20}$ −177° (75% alcohol, c = 0.92).

Anal. Calc'd for $C_{39}H_{48}I_2N_2O_6 + 2H_2O$: C, 50.33; H, 5.63; H_2O, 3.86.
Found: C, 49.82; H, 5.47; H_2O, 4.28.

The *monosemicarbazone* was prepared by refluxing 0.75 g. of 7,7′-methylenebisdihydrocodeinone, 2.0 g. of semicarbazide hydrochloride, and 1 ml. of pyridine in 25 ml. of methanol for one hour. After standing overnight, the solution was evaporated under reduced pressure and the residue taken up in 50 ml. of water. Basifying with concentrated ammonia gave a precipitate which was recrystallized by dissolving in ethanol and adding water until the warm solution became cloudy. Cooling gave crystals, m.p. 218–220° with preliminary softening, $[\alpha]_D^{20}$ −383° (alcohol, c = 0.512).

Anal. Calc'd for $C_{38}H_{45}N_5O_6$: C, 68.34; H, 6.79; N, 10.49.
Found: C, 67.81; H, 6.76; N, 9.83.

SUMMARY

The Mannich reaction with dihydrocodeinone and 1-bromodihydrocodeinone is found to yield 7,7′-methylenebis compounds instead of the usual dialkylaminomethyl derivatives.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH AND THE UNIVERSITY OF VIRGINIA]

THE PHENYLDIHYDROTHEBAINES

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In a recent publication on the methyldihydrothebaines, Small and Fry (1) pointed out in detail the inexplicable peculiarities of phenyldihydrothebaine, and demonstrated that these remarkable properties are also shown by the four isomeric methyldihydrothebaines. These peculiarities are, briefly, resistance to hydrogenation, resistance of the enol ether group to hydrolysis, and retention of the vinyl group in the final step of exhaustive methylation. While their work did not result in a satisfactory structural formula for this type of thebaine derivative, it did establish the fact that the peculiarities mentioned are not the result of some specific influence (steric or "negative") of the phenyl group. The appearance of isomeric methyldihydrothebaines in the Grignard reaction led to the prediction (ref. 1, page 513, footnote) that the hitherto-known phenyldihydrothebaine (2, 3, 4) must be a mixture of isomers. With the object of settling this point, as well as to obtain additional structural evidence, the long-dormant phenyldihydrothebaine problem has been reopened.

THE ISOMERS

The reaction of thebaine (I) with phenylmagnesium bromide in ether, or preferably in benzene because of better solubility and more rapid reaction, gives a sirupy product which constitutes the so-called "phenyldihydrothebaine." This can be separated through the hydrochloride into two isomeric compounds of formula $C_{25}H_{27}NO_3$, differing empirically from thebaine, $C_{19}H_{21}NO_3$, by C_6H_6. The major product, obtained in a yield of 75-78% is named (+) α-phenyldihydrothebaine (II), in analogy with the methyl series. The minor product, yield 7-8% is (+) δ-phenyldihydrothebaine (III). Although the two compounds are identical in molecular formula, they have different physical properties, as do their salts and primary degradation products. They are phenolic (alkali solubility, diazosulfanilic acid reaction), and, as would be expected, show the same abnormalities as the mixture that had been studied by all previous investigators. Neither base can be hydrogenated in a normal manner like the parent thebaine (the reduction to phenyltetrahydrothebaimine described later is a degradative reduction), nor hydrolyzed at the 6-methoxyl (enol ether?) group by boiling concentrated hydrolchloric acid.

As in the methyldihydrothebaine series, (+) α-phenyldihydrothebaine can be caused to isomerize by very slow distillation in a high vacuum, or by heating in an evacuated sealed tube at 200° for 80 hours. About 75% of the α base is recovered, together with 16% of a new phenyldihydrothebaine which is the optical opposite of the (+) δ-phenyldihydrothebaine described above, and will therefore be designated as (−) δ-phenyldihydrothebaine (IV). Its physical properties and those of its derivatives are identical with those of the corresponding (+) δ compounds except that optical rotations are equal and opposite in direction. The new isomer corresponds to the "η-methyldihydrothebaine" of Small and Fry.[3] The transformation is probably an equilibrium reaction lying largely in the (+) α direction, for if pure (−) δ-phenyldihydrothebaine is subjected to the same treatment, 57% yield of (+) α-phenyldihydrothebaine is obtained and only traces of the starting material.

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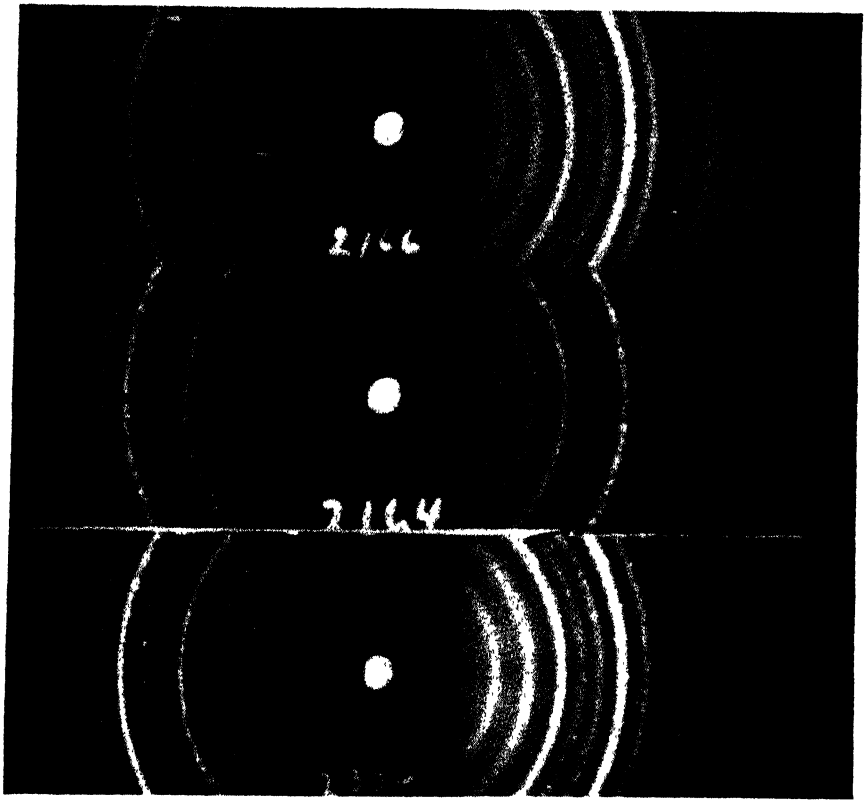

Fig. 1. X-Ray Diffraction Patterns, 2166, (+) α-Phenyldihydrothebaine Perchlorate; 2164, (−) α-Phenyldihydrothebaine Perchlorate; 2356, (+) α-Phenyldihydrothebaine Perchlorate from Rearrangement of (−) δ Phenyldihydrothebaine

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[3] The unfortunate nomenclature for the optical opposites was adopted at that time through over caution in interpreting the transformation. Since assignment of the Greek letters is at best arbitrary, the δ title is retained to avoid further complicating a confused situation. This introduces the anomaly that some compounds designated as (+) are actually levorotatory, and vice versa.

When (+) δ-phenyldihydrothebaine (III) is treated in like manner, a fourth isomer, (−) α-phenyldihydrothebaine (V) results (corresponding to "ω-methyldihydrothebaine"). This is the optical antipode of (+) α-phenyldihydrothebaine. As indicated above, the equilibrium seems to be in favor of the α types, for this rearrangement gives 74% yield of (−) α and 24% recovery of (+) δ. Scarcity of material prevented demonstration of the reverse rearrangement of (−) α to (+) δ. In no instance did these rearrangements give rise to molecular compounds of the type observed in the methyl series, nor did the pairs of antipodes give crystalline racemates, although some of their degradation products did.

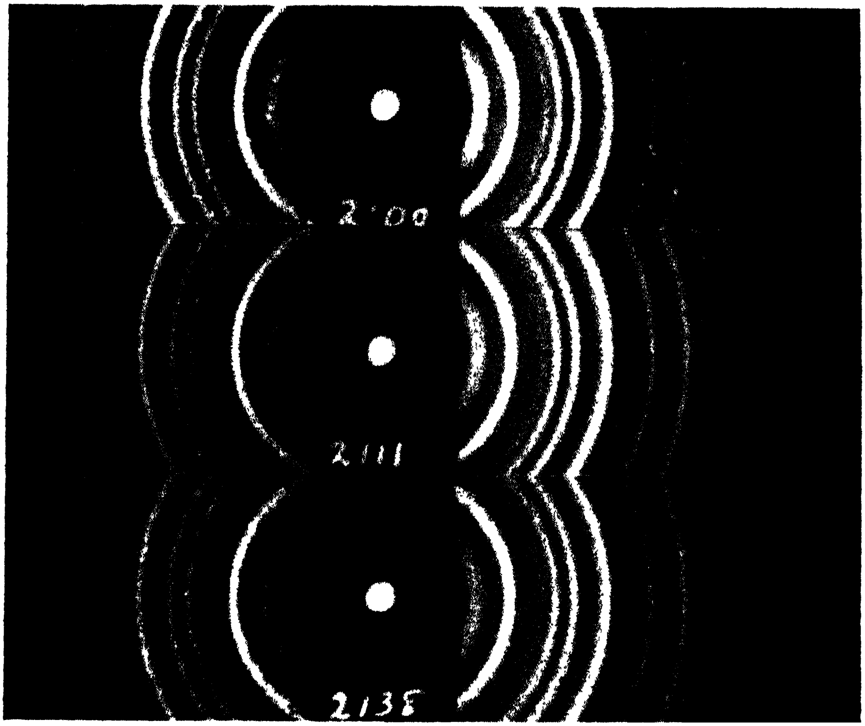


Fig. 2. x-Ray Diffraction Patterns; 2100, + δ-Phenyldihydrothebaine; 2111, (−) δ-Phenyldihydrothebaine; 2138, (+) δ,(−) δ Mixed Crystal

In support of the evidence for optical isomerism given by melting points and rotatory values of these bases and their derivatives, we have examined x-ray diffraction patterns, which for optical opposites must of course be identical. Since the α bases are liquids, we show in Fig. 1 the patterns of (+) and (−) α-phenyldihydrothebaine perchlorates, and also the pattern of the (+) α-perchlorate obtained by rearrangement of (−) δ-phenyldihydrothebaine; apart from other physical properties recorded, the identity is obvious. Fig. 2 shows the patterns of the (+) and (−) δ bases, and of a recrystallized mixture of equal amounts of these, where racemate formation did not take place. The properties of the four isomers and some of their derivatives are summarized in Table I. We wish to

TABLE I

PHYSICAL PROPERTIES OF THE ISOMERIC PHENYLDIHYDROTHEBAINES AND SOME DERIVATIVES

NAME	BASE		PERCHLORATE		METHIODIDE	
	M.P., °C.	$(\alpha)_D$	M.P., °C.	$(\alpha)_D$	M.P., °C.	$(\alpha)_D$
(+) α-Phenyldihydrothebaine (II)	liq'd	+10.2	248 d.	+8.2^a +35	216–218	+42.7
(−) α-Phenyldihydrothebaine (V)	liq'd	−10	248 d.	−8.0^a −35	216	−43.6
(+) αPhenyldihydrothebaine isomethine (XXI)	101	−280	111–117^b	−197		
(−) α-Phenyldihydrothebaine isomethine (XXXIII)	101	+281	111–116^b	+197		
(+) δ-Phenyldihydrothebaine (III)	143.5	−131^a −109	209–213	−44.5	206–208	−43
(−) δ-Phenyldihydrothebaine (IV)	143.5	+131^a +110	209–213	+42.8	206–208	+44
(+) δ-Phenyldihydrothebaine isomethine (IX)	117–119	+153	114–116^b	+89.6	202–203	+108
(−) δ-Phenyldihydrothebaine isomethine (XXX)	117–119	−154	111–116^b	−90.0	202–203	−105
(+) Phenyltetrahydrothebaimine (VIII)	120–121	−35.0^a −4.2			235^c	−5.2
(−) Phenyltetrahydrothebaimine (XIII)	120–120.5	+35.5^a +4.9			235^c	+5.3
rac. Phenyltetrahydrothebaimine (XIV)	131	0.0				
(+) Hexahydrophenyltetrahydrothebaimine (XVI)	129–130.5	−9.0			231–232.5	−1.8
(−) Hexahydrophenyltetradrothebaimine (XXXI)	128–129.5	−10.0			231–232	+6.6
(+) Vinylphenyldihydrothebaol (XIX)	119	+47.1				
(−) Vinylphenyldihydrothebaol (XXIII)	147–148.5	−47.4				
rac. (?) Vinylphenyldihydrothebaol (XXIV)	146–147	0.0				

^{a} Rotations in different solvents.
^{b} Solvated.
^{c} N-methomethiodide.

emphasize at this point that the designations (+) and (−) are based entirely on derivation, and relationship to the methyl series, and not on actual direction of rotation, since in many transformations the rotational direction is reversed. Furthermore, the structural formulas given are based on the arbitrary assumption of a 1,4-addition of the Grignard reagent, and are offered only as illustrative of the changes taking place in reactive portions of the molecule.

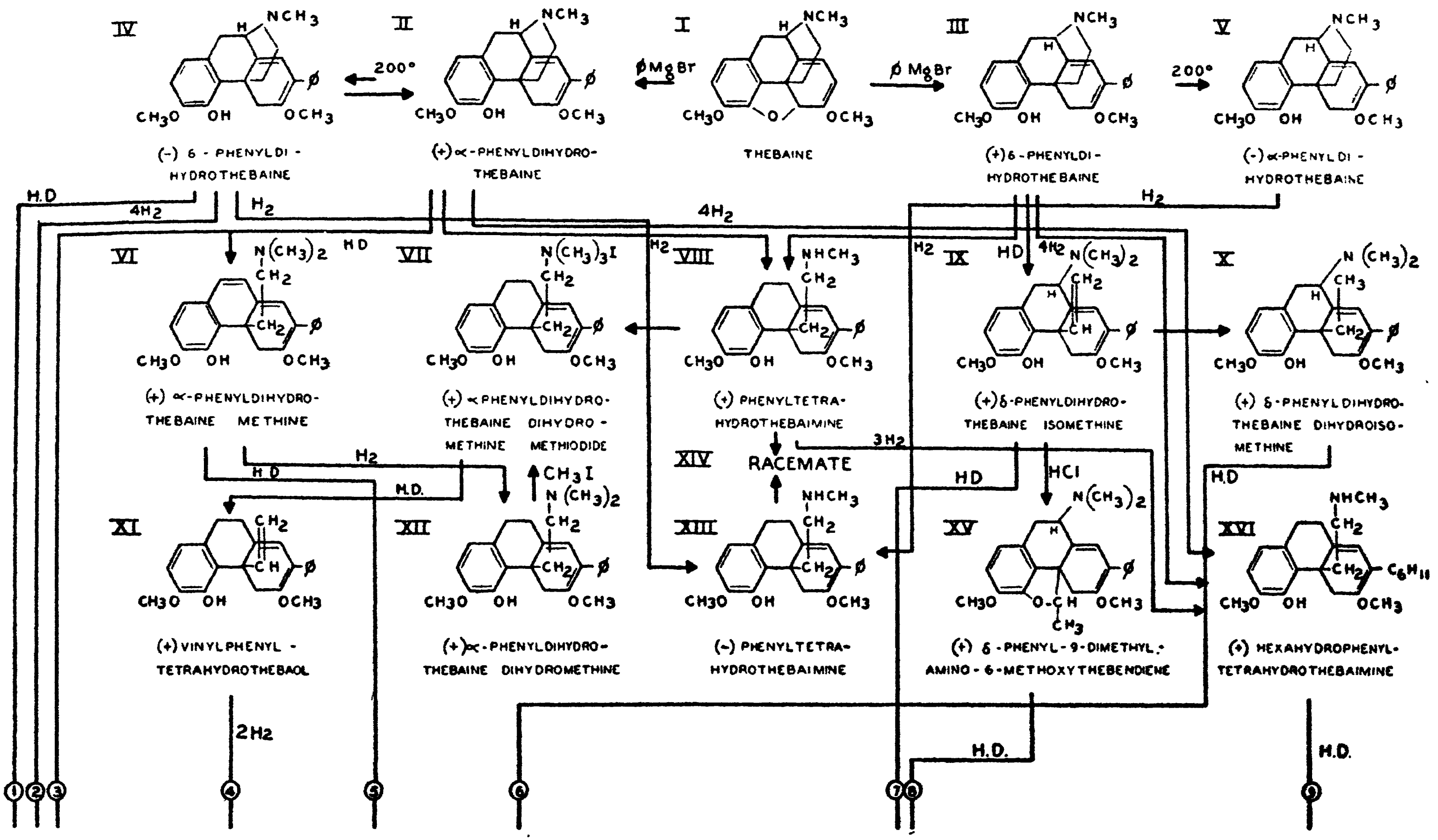
DEGRADATION OF THE PHENYLDIHYDROTHEBAINES

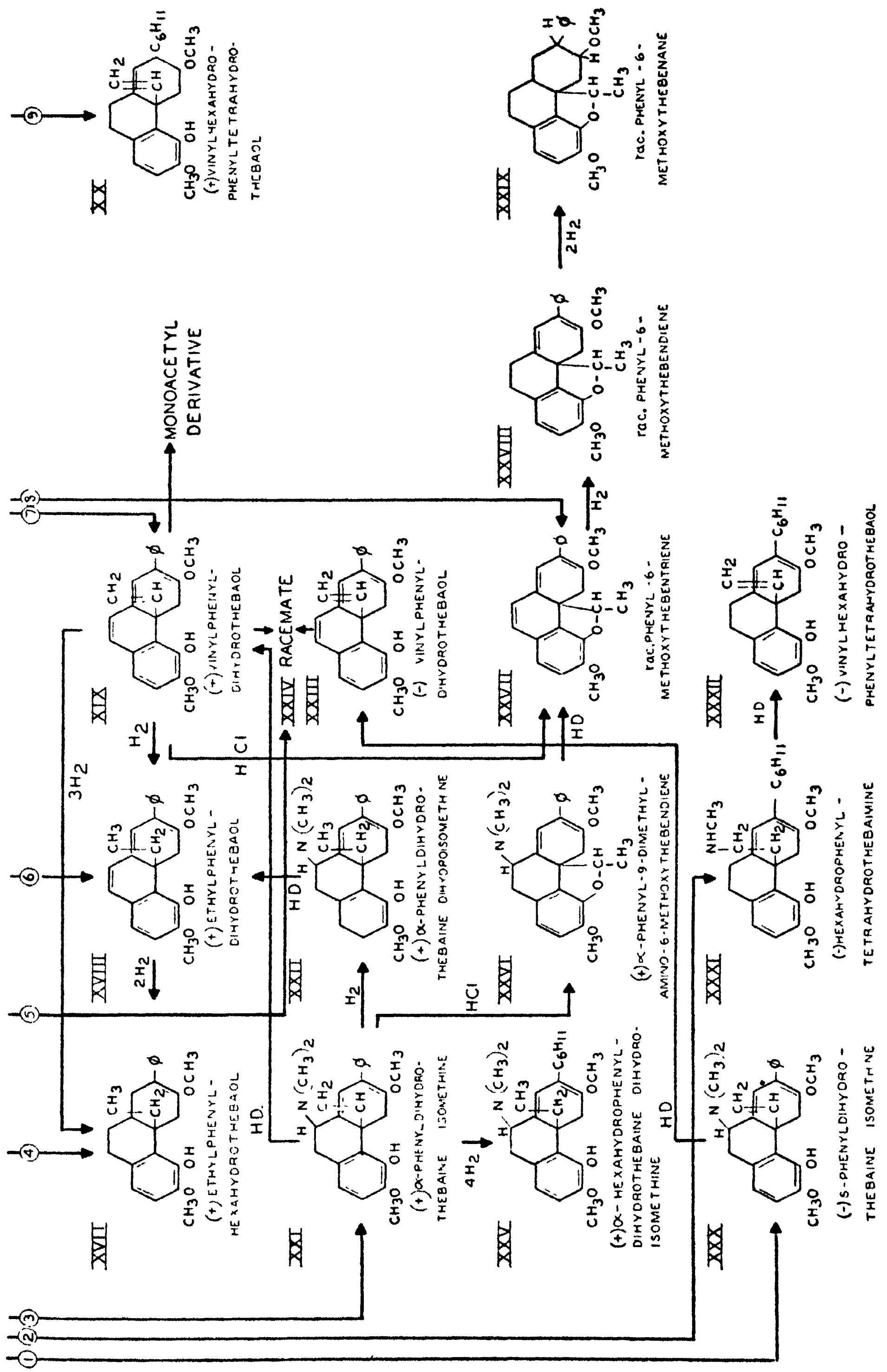
The degradation of the phenyldihydrothebaines proceeds parallel to that of the methyl analogs, and furnishes strong support for the interpretation of the results in that series. Although the phenyl types are more resistant to alkaline degradation, all except the rare (−) α isomer have been converted to the nitrogen-free end-products. Like the methyl analogs, the phenyldihydrothebaines undergo rupture of the nitrogen-containing ring chiefly in the abnormal manner to give isomethines, with nitrogen still attached to C-9, and carbons 15 and 16 in the form of a vinyl group. No other morphine derivatives containing the typical carbon-nitrogen morphine skeleton have ever been observed to break down in this way. This is an important consideration, which may indicate a fundamental structural change. On the other hand, in the majority of degradations recorded (see ref. 5, pp. 285, 286) the basic product in the final step was not identified, or recorded only as trimethylamine; only in those where β-hydroxyethyldimethylamine or a similar fragment was identified is it certain that the normal mechanism was involved. It should be pointed out here, that this initial abnormal course of the first step in the Hofmann degradation cannot be considered responsible for the anomalous retention of the vinyl group in the second step, for the normal methine type (a minor product from the first step) likewise breaks down (VI → XXIV) to a nitrogen-free product which still carries these two carbon atoms.

The Hofmann degradation of (+) α-phenyldihydrothebaine methiodide results in 72% yield of the isomethine (XXI), 14% undegraded base (presumably by splitting off methanol, which is not uncommon), and 3% of the normal methine (VI). This is the only instance in which both methines were isolated. The isomeric methines can be differentiated by their behavior towards boiling concentrated hydrochloric acid; the normal methine is entirely unaffected, whereas the vinyl group of the isomethine undergoes cyclization with the 4-hydroxyl to give (+) α-phenyl-9-dimethylamino-6-methoxythebendiene (XXVI), which, in contrast to the isomethine, is no longer phenolic, and is indifferent towards catalytic hydrogenation. This reaction is similar to that observed in the methyldihydrothebaines, where Small and Fry demonstrated that the mechanism involved addition of the elements of water to the vinyl group, followed by cyclodehydration. In agreement with this concept, the hydrogenated (one mole) isomethine (XXII), which has an ethyl group in place of vinyl, is unchanged by the acid treatment.

Further degradation of the cyclized isomethine (XXVI) results in a non-phenolic, optically inactive, nitrogen-free product, *rac.* phenyl-6-methoxythebentriene (XXVII). The thebentriene takes up one mole of hydrogen in neutral medium (presumably at the 9,10 unsaturation), to give XXVIII, and two addi-

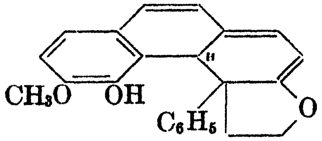
TRANSFORMATIONS OF THE PHENYLDIHYDROTHEBAINES


IV
(-) δ - PHENYLDI - HYDROTHEBAINE
II
(+) α - PHENYLDIHYDRO- THEBAINE
I
THEBAINE
III
(+) δ - PHENYLDI - HYDROTHEBAINE
V
(-) α - PHENYLDI - HYDROTHEBAINE
200°
ϕ MgBr
VI
(+) α - PHENYLDIHYDRO- THEBAINE METHINE
VII
(+) α PHENYLDIHYDRO- THEBAINE DIHYDRO - METHINE METHIODIDE
VIII
(+) PHENYLTETRA- HYDROTHEBAIMINE
IX
(+) δ - PHENYLDIHYDRO- THEBAINE ISOMETHINE
X
(+) δ - PHENYLDIHYDRO- THEBAINE DIHYDROISO- METHINE
XIV
RACEMATE
XI
(+) VINYLPHENYL - TETRAHYDROTHEBAOL
XII
(+) α - PHENYLDIHYDRO- THEBAINE DIHYDROMETHINE
XIII
(-) PHENYLTETRA- HYDROTHEBAIMINE
XV
(+) δ - PHENYL - 9 - DIMETHYL - AMINO - 6 - METHOXYTHEBENDIENE
XVI
(+) HEXAHYDROPHENYL- TETRAHYDROTHEBAIMINE
H.D
4H2
H2
HD
4H2
3H2
HCl
CH3I
2H2
H.D.
① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨


①
②
③
④
⑤
⑥
⑦
⑨
XVII
(+) ETHYLPHENYL-HEXAHYDROTHEBAOL
2H2
3H2
XVIII
(+) ETHYLPHENYL-DIHYDROTHEBAOL
H2
XIX
(+) VINYLPHENYL-DIHYDROTHEBAOL
MONOACETYL DERIVATIVE
XX
(+) VINYLHEXAHYDRO-PHENYLTETRAHYDRO-THEBAOL
HD
XXI
(+) α-PHENYLDIHYDRO-THEBAINE ISOMETHINE
H2
XXII
(+) α-PHENYLDIHYDRO-THEBAINE DIHYDROISOMETHINE
HCl
XXIV RACEMATE
XXIII
(-) VINYLPHENYL-DIHYDROTHEBAOL
4H2
XXV
(+) α-HEXAHYDROPHENYL-DIHYDROTHEBAINE DIHYDRO-ISOMETHINE
HCl
XXVI
(+) α-PHENYL-9-DIMETHYL-AMINO-6-METHOXYTHEBENDIENE
HD
XXVII
rac. PHENYL-6-METHOXYTHEBENTRIENE
H2
XXVIII
rac. PHENYL-6-METHOXYTHEBENDIENE
2H2
XXIX
rac. PHENYL-6-METHOXYTHEBENANE
HD
XXX
(-) δ-PHENYLDIHYDRO-THEBAINE ISOMETHINE
XXXI
(-) HEXAHYDROPHENYL-TETRAHYDROTHEBAIMINE
HD
XXXII
(-) VINYLHEXAHYDRO-PHENYLTETRAHYDROTHEBAOL

tional moles in acid medium, *rac.* phenyl-6-methoxythebenane (XXIX). A stepwise reduction of the external phenyl group seems excluded, so we are now faced with the question, why has it suddenly become possible to hydrogenate ring III, whereas the isomethine itself is so resistant at this point that forcing the hydrogenation (platinum oxide, hydrochloric acid) apparently even saturates the phenyl group (XXV) without affecting the alicyclic double bonds?

When uncyclized (+) α-phenyldihydrothebaine isomethine is degraded by the Hofmann method, a phenolic, dextrorotatory, nitrogen-free product, (+) vinylphenyldihydrothebaol (XIX) is obtained. This is identical in physical properties with a compound prepared by Freund (2) by the same method, and designated as phenyldihydrothebenol (XXXIV).



XXXIV. Phenyldihydrothebenol (Freund, 1905)

Probably because of the extremely low solubility of this substance in hydriodic acid (our first analysis, conducted as usual, showed more than one but less than two methoxyls), Freund found only one methoxyl group present, and sought to explain this by postulating hydrolysis of the 6-methoxyl, followed by cyclization with the vinyl group (at that time thought to be at C-5). Both combustion analysis and Zeisel (conducted with sufficient acetic anhydride to ensure solution) show the presence of two methoxyl groups, and phenyldihydrothebenol should therefore be deleted from the literature. The phenolic properties, and formation of a monoacetyl derivative show that the 4-hydroxyl group in the thebaol (XIX) has not been involved in a cyclization, and further proof that the vinyl group is unchanged, in contrast to Freund's claim, lies in the fact that boiling hydrochloric acid causes cyclization, and yields the above-described *rac.* phenyl-6-methoxythebentriene (XXVII). For unknown reasons, the acid treatment demethylates the nitrogen-free compound, and the strongly phenolic, optically active product must be remethylated and racemized with sodium ethoxide before XXVII is obtained.

In neutral solution XIX adds one mole of hydrogen at the vinyl group, as is shown by the fact that the same product, (+) ethylphenyldihydrothebaol (XVIII) is obtained when (+) α-phenyldihydrothebaine isomethine (XXI) is reduced at the vinyl group, (+) α-phenyldihydrothebaine dihydroisomethine (XXII), and subsequently degraded.

The reduction of (+) vinylphenyldihydrothebaol in acid solution is peculiar; two moles of hydrogen are taken up rapidly, presumably at the vinyl group and the 9,10-unsaturation, and a third mole is then added very slowly, and the hydrogenation stops, (+) ethylphenylhexahydrothebaol (XVII). Probably the ring double bond not involved in the enol ether group has been saturated. The same compound results from addition of two moles of hydrogen (one rapidly, one slowly) to the above-described (+) ethylphenyldihydrothebaol (XVIII), which excludes the external phenyl group as the acceptor of hydrogen. This constitutes the second example of an apparent (partial) reduction of ring III in a nitrogen-free product.

(+) α-PHENYLDIHYDROTHEBAINE NORMAL METHINE (VI)

This minor product from the first step of the Hofmann degradation has the heterocyclic ring opened in the manner expected for the morphine series, and hence is referred to as the normal methine. Its methohydroxide breaks down with such difficulty that dry vacuum-distillation must be resorted to, so that it is not surprising that the product is optically inactive. *rac.* Vinylphenyldihydrothebaol (XXIV) contains a phenolic hydroxyl and two methoxyls, and is isomeric with the dextro compound from the degradation of the isomethine; it will be mentioned again in the discussion of (−) δ-phenyldihydrothebaine.

(+) α-Phenyldihydrothebaine normal methine adds one mole of hydrogen at the 9,10-unsaturation to give a dihydro derivative (XII), whose methiodide (VII) is identical with the N-methomethiodide of phenyltetrahydrothebaimine (VIII), a point of great importance for the structure of that compound.

(+) δ-PHENYLDIHYDROTHEBAINE (III)

The Hofmann degradation of (+) δ-phenyldihydrothebaine gives a crystalline isomethine (IX) in 58% yield; the normal methine, if present, could not be isolated in the small scale necessitated by the rarity of material. The isomethine, like the (+) α analog, undergoes cyclization with hydrochloric acid, giving (+) δ-phenyl-9-dimethylamino-6-methoxythebendiene (XV), a diastereoisomer of the cyclization product in the (+) α series. The second step of the degradation, elimination of the nitrogen atom, gives *rac.* phenyl-6-methoxythebentriene (XXVII). Similarly, when the uncyclized isomethine (IX) is further degraded, the product is (+) vinylphenyldihydrothebaol (XIX), identical in every respect with that obtained from the degradation of (+) α-phenyldihydrothebaine isomethine. Since the isomerism between the (+) α and the (+) δ series disappears with the elimination of the asymmetry at C-9, it follows that the (+) α and (+) δ compounds differ only in the configuration at this point. This is in agreement with the observations in the methyldihydrothebaine series. Furthermore, if the (+) δ-isomethine is reduced at the vinyl group (X), and then degraded, the product is the same (+) ethylphenyldihydrothebaol (XVIII) that is obtained from the parallel reaction in the (+) α series. Additional evidence on the isomerism of the (+) α and (+) δ compounds will be offered in the discussion of phenyltetrahydrothebaimine.

(−) α-PHENYLDIHYDROTHEBAINE (V)

This isomer, from rearrangement of the not-abundant (+) δ form, was not obtained in sufficient quantity for complete degradation. It was characterized as the perchlorate and methiodide. The latter undergoes degradation to a mixture of methine bases, from which the (−) α isomethine can be obtained pure, but the very soluble normal methine cannot be separated. That the relationship of the (−) α-phenyldihydrothebaine to the (−) δ isomer is the same as has been demonstrated for the (+) series is amply shown by the transformation to the (−) phenyltetrahydrothebaimine discussed below.

(−) δ-PHENYLDIHYDROTHEBAINE (IV)

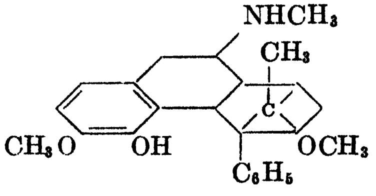
Degradation of (−) δ-phenyldihydrothebaine, as would be expected, since no asymmetric center is disturbed, yields an isomethine (XXX) that is the enantiomorph of (+) δ-phenyldihydrothebaine isomethine (IX), but a diastereoisomer of the (+) and (−) α-isomethines (XXI and XXXIII). This fact furnishes further confirmation of the mechanism of isomethine formation.

On completing the degradation, destroying the asymmetry at C-9, a (−) vinylphenyldihydrothebaol (XXIII) results that is the optical opposite of the degradation product from the (+) α- and (+) δ-isomethines, and combines with it to give the same racemic (?) vinylphenyldihydrothebaol (XXIV) that is obtained by dry distillation of (+) α-phenyldihydrothebaine normal methine methohydroxide. The (+) α and (+) δ pair evidently differ from the (−) α, (−) δ pair in having opposite configuration at the asymmetric center(s) remaining in the nitrogen-free degradation products.

THE PHENYLTETRAHYDROTHEBAIMINES

The conclusion reached above concerning the nature of the isomerism of the (+) α and (+) δ-phenyldihydrothebaines involves the tacit assumption that elimination of nitrogen takes place as usual in the morphine series, with creation of a double bond at C-9, C-10. It is however possible that the double bond might be formed between C-9 and C-14 (if C-14 is not already unsaturated or blocked), in which case either or both of these centers could be responsible for the isomerism. This possibility can now be excluded, both by spectral and chemical evidence.

Freund (3) first observed that reduction of phenyldihydrothebaine (mixture) in dilute acetic acid with colloidal palladium proceeds with absorption of one mole of hydrogen, involving reductive scission of the ethanamine chain. The product is a secondary amine, phenyltetrahydrothebaimine (VIII), and is one of the few pure substances that Freund had in his hands. From evidence involving his false concept of the structure of "phenyldihydrothebenol", Freund interpreted this degradative reduction as a rupture between the nitrogen and C-16 (XXXV).



XXXV. Phenyltetrahydrothebaimine (Freund, 1916)

We have proved it to be, instead, a break between nitrogen and C-9. The N-methomethiodide (VII) of phenyltetrahydrothebaimine is in every way identical with the methiodide of (+) α-phenyldihydrothebaine normal dihydromethine. Furthermore, we find that both (+) α- and (+) δ-phenyldihydrothebaine yield the *same* (+) phenyltetrahydrothebaimine. It is not possible that a break between C-16 and nitrogen could result in elimination of the isomerism; the destruction of the asymmetry at C-9 is in agreement with the proof already adduced from the Hofmann degradation, that the configuration at C-9 is solely responsible for the isomerism of this pair. In addition, (−) α- and (−) δ-phenyldihydrothebaines, reduced under the same conditions, yield a single (−) phenyltetrahydrothebaimine (XIII), the optical antipode of the one discussed above, with which it forms a racemate (XIV) of higher melting point, lower solubility, and zero rotation. Hence, the (−) α and (−) δ isomers also differ only in the configuration at C-9, and have the opposite configuration from the (+) α and (+) δ pair at the asymmetric center(s) other than C-9. Figures 3 and 4 demonstrate the identity of crystal form of the (+) and (−) phenyltetrahydrothebaimines, and Fig. 5 shows the entirely different crystal habit of the racemate. Optical crystallographic examination (Dr. Geo. L. Keenan) of the isomers gives identical data, and shows the racemate to have quite different properties (see Experimental Part). In Fig. 6 the identical x-ray diffraction patterns of the isomers are contrasted with that of the racemate.

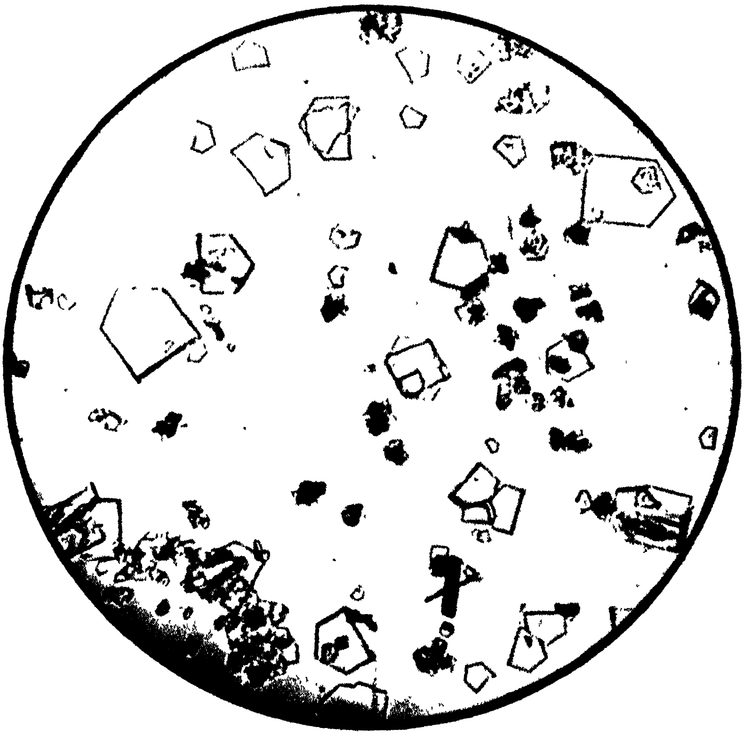


FIG. 3 (+) PHENYLTETRAHYDROTHEBAIMINE

(+) Phenyltetrahydrothebaimine N-methomethiodide (VII) undergoes alkaline degradation in a single step to (+) vinylphenyltetrahydrothebaol (XI), a compound isomeric with (+) ethylphenyldihydrothebaol (XVIII) obtained from (+) α-phenyldihydrothebaine dihydroisomethine (XXII). Had phenyltetrahydrothebaimine the Freund structure, these two must be identical. It is clear that they differ only by the position of one double bond (vinyl group and C-9,10) as required by our formulation of phenyltetrahydrothebaimine, for on hydrogenation (as the acetyl derivative), both give the same acetyl (+) ethylphenylhexahydrothebaol (acetyl-XVII). It may be remarked that Freund degraded phenyltetrahydrothebaimine to a "phenyltetrahydrothebenol" (m.p. the same as that of XI), in which he found two methoxyl groups still present; he did not comment on the fact that the supposed cyclization with splitting of the 6-methoxyl failed to take place in this instance (probably because of the false structural concept shown in XXXV).

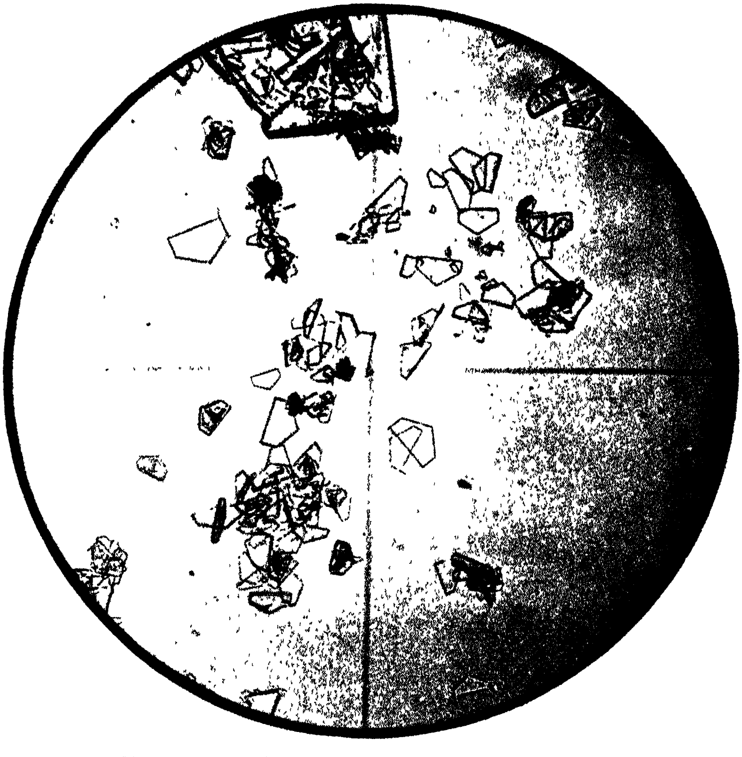


Fig. 1. (−) Phenyltetrahydrothebaimine

(+) Phenyltetrahydrothebaimine can be further reduced in acid solution with platinum oxide. Three moles of hydrogen are absorbed, presumably at the external phenyl group, since this is the only reducible system of three double bonds present (ring I of the morphine series has never been reduced; moreover, the product is still phenolic). (+) Hexahydrophenyltetrahydrothebaimine (XVI) can also be made directly from either (+) α or (+) δ-phenyldihydrothebaine by addition of four moles of hydrogen. (−) δ-Phenyldihydrothebaine, as expected, reduces under these conditions to (−) hexahydrophenyltetrahydrothebaimine (XXXI), the optical opposite of the product from the (+) α and (+) δ isomers. The nitrogen-free products from degradation of these (+) and (−) hexahydrophenyltetrahydrothebaimines are also optical opposites, phenolic, with two methoxyl groups, and will be called (+) and (−) vinylhexahydrophenyltetrahydrothebaol, respectively, XX and XXXII. Attempts to verify reduction of the external phenyl group by preparation of a cyclohexyldihydrothebaine were not successful. Although thebaine reacts with cyclohexylmagnesium bromide, the product is a sensitive (oxidation?), highly colored resin, from which no definite compound could be isolated.

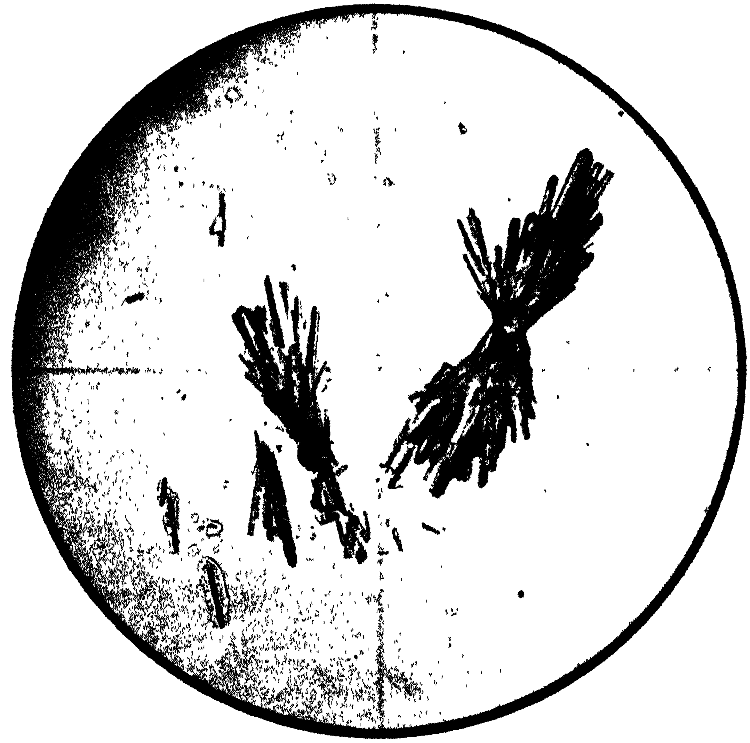


FIG. 5 *rac* PHENYLTETRAHYDROTHEBAIMINE

The parallel hydrogenation of (+) α-phenyldihydrothebaine isomethine proceeds with absorption of four moles of hydrogen, one at the vinyl group, and three presumably at the phenyl group, to give an isomeric compound, (+) α-hexahydrophenyldihydrothebaine dihydroisomethine (XXV).

NORPHENYLDIHYDROTHEBAINE

In a brief investigation, not published beyond a dissertation, H. Hoek (6) observed that completely O-demethylated phenyldihydrothebaine behaves as though it contains three phenolic hydroxyl groups. We have verified Hoek's work; demethylation with hydrobromic acid gives a well-characterized methoxyl-free base, which reacts with diazomethane to give a trimethyl ether which is identical with that resulting from the action of this reagent on phenyldihydrothebaine itself. This might be explained by assuming a keto-enol tautomerism at C-6, but like Hoek, we were unable to obtain an oxime from norphenyldihydrothebaine, which should be possible if such a tautomerism existed. This demethylation, which proceeds in 85% yield, offers another example of the extraordinary stability of the ring system in phenyldihydrothebaine, in contrast to that of thebaine, which is destroyed almost completely by a few minutes boiling with normal sulfuric acid, or even potassium acid sulfate solution. Norphenyldihydrothebaine deserves further study.

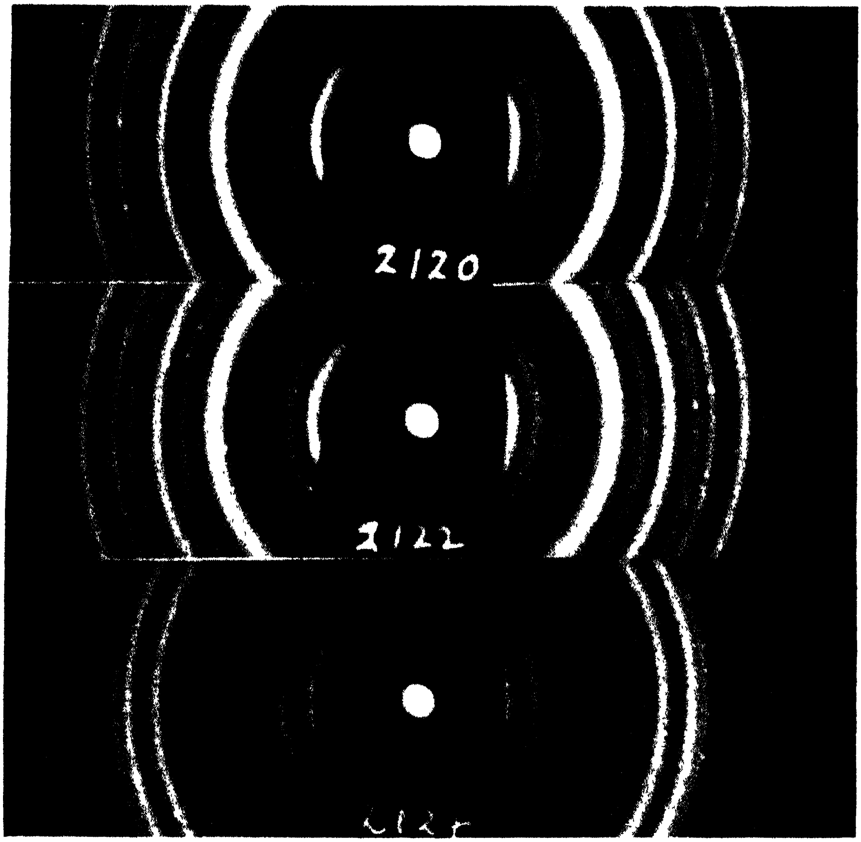


FIG. 6. x-RAY DIFFRACTION PATTERNS; 2120, (+) PHENYLTETRAHYDROTHEBAIMINE; 2122, (−) PHENYLTETRAHYDROTHEBAIMINE; 2124, *rac.* PHENYLTETRAHYDROTHEBAIMINE

DISCUSSION

In the foregoing description, we have demonstrated in four distinct ways that the (+) α, (+) δ pair and the (−) α, (−) δ pair of isomers owe their isomerism to a configurational difference at C-9; namely, degradation of (+) α- and (+) δ-isomethines to the same (+) vinylphenyldihydrothebaol (XXI, IX, → XIX); degradation of (+) α- and (+) δ-dihydroisomethines to (+) ethylphenyldihydrothebaol (XXII, X, → XVIII); degradative hydrogenation of (+) α- and (+) δ-phenyldihydrothebaines to (+) phenyltetrahydrothebaimine (II, III, → VIII); and the parallel conversion of (−) α- and (−) δ-phenyldihydrothebaines to (−) phenyltetrahydrothebaimine (V, IV, → XIII). The last two examples also show that the (+) α, (+) δ pair differ from the (−) α, (−) δ pair in having the opposite configuration at the other asymmetric center(s). It is striking that all of the examples indicate that the interconversion of the isomers is through racemization of C-13 (?), never C-9.

On the other hand, the appearance of (+) δ-phenyldihydrothebaine along with (+) α-phenyldihydrothebaine in the Grignard reaction implies a racemization of C-9 *during* the reaction. How can phenylmagnesium bromide, obviously engaged in opening the ether ring, affect such a remote center? It is not an effect of the reagent in racemizing at this point in the α-compound after its formation, for pure α-phenyldihydrothebaine, on prolonged boiling in benzene with phenylmagnesium bromide, yields no trace of the isomer.

If one is willing to admit the possibility of a trans ring in such a structure as that of thebaine (or that the thebaine formula is fundamentally incorrect), there remains an explanation for the formation of the (+) δ isomer which must be considered, but which we suggest with reluctance; namely, that thebaine is not a single substance, and may already contain a certain amount of an isomer with inverted configuration at C-9. Tentative experiments on the separation of such an isomer from thebaine by physical and chemical methods have so far failed.

It will be noted that Small and co-workers (7, 8) observed some years ago that the reaction of methyl-, ethyl-, and phenyl-magnesium halides with dihydrothebaine resulted in the formation of isomeric nuclear-substituted dihydrothebainones, whereas the action of methylmagnesium iodide on dihydrocodeinone enol acetate (*ex* codeine) gave only one methyldihydrothebainone. This seemed at first to offer some support to the hypothesis advanced above, but further investigation shows that the isomerism in the methyldihydrothebainone series is not of the same type as that of the methyl- and phenyl-dihydrothebaines. Degradation of methyldihydrothebainone, and isomethyldihydrothebainone, gives in the first step different methine bases, and in the second step, where isomerism should disappear if it is due to C-9, entirely different, isomeric nitrogen-free end-products.

The extreme resistance of phenyldihydrothebaine to normal catalytic hydrogenation is not without parallel in the morphine series, and in every instance known to us, the recalcitrant compounds have arisen from the Grignard reaction. Small and Yuen (9) prepared a series of alkyl and aryl substituted derivatives from desoxycodeine-C, in which the ether ring was opened, and the organic residue of the reagent added. These could be hydrogenated (one mole) with difficulty in acid solution, which was assumed to be saturation of the double bond. Reinvestigation of one of these hydrogenation products still available, that from phenyldihydrodesoxycodeine, shows it to be a secondary amine, *i.e.*, the supposed reduction of the double bond was actually a degradative reduction like that which results in the phenyltetrahydrothebaimines.

Small, Turnbull, and Fitch (8) observed that the phenolic product obtained from methylmagnesium iodide and pseudocodeine methyl ether resisted hydrogenation under widely varied conditions. Similarly, the phenolic compound from methylmagnesium iodide and pseudocodeinone could not be hydrogenated, nor did it give any of the reactions for a carbonyl group (10).

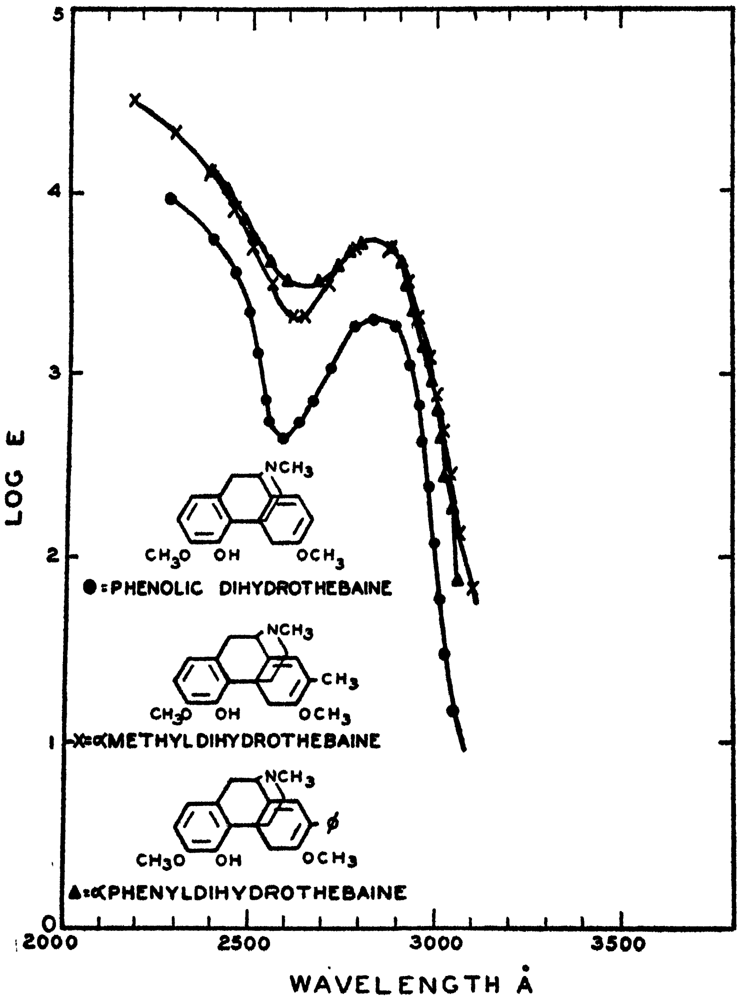


FIG. 7. ULTRAVIOLET ABSORPTION SPECTRA OF PHENOLIC DIHYDROTHEBAINE, α-METHYLDIHYDROTHEBAINE, AND (+) α-PHENYLDIHYDROTHEBAINE

The generally accepted morphine and thebaine formulas do not offer any reasonable explanation of these facts, nor of the phenomena described in this communication. The unquestionable retention of the vinyl group in the degradation of the phenyldihydrothebaines is particularly disturbing, since the characteristic tendency of (ring) unhydrogenated morphine derivatives to revert to aromatic (phenanthrene) systems through extrusion of this group constitutes one of the chief arguments for the Gulland and Robinson morphine formula.

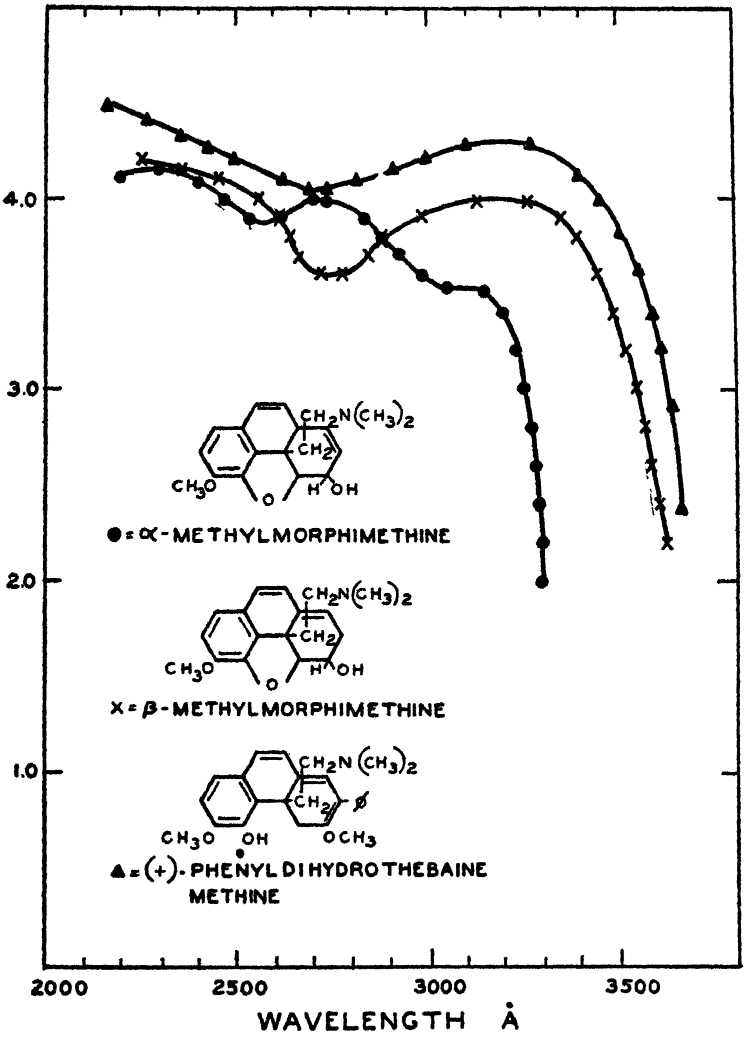


Fig. 8. Ultraviolet Absorption Spectra of (+) α-Phenyldihydrothebaine Normal Methine, β-Methylmorphimethine, and α-Methylmorphimethine

There remains, of course, the possibility that the Grignard reaction has caused deeper-seated changes in the thebaine molecule than we have assumed. We have sought evidence on this point by comparison of the ultraviolet absorption spectra of methyldihydrothebaine and phenyldihydrothebaine with that of the most closely related thebaine derivative in which it is certain that there has been no fundamental structural change, namely, the phenolic dihydrothebaine[4] of Small and Browning (11). As shown in Fig. 7, the three compounds show maxima and minima at almost identical wavelengths. Furthermore, the absorption curves for β-methylmorphimethine and phenyldihydrothebaine normal methine (Fig. 8) are closely similar, whereas that for α-methylmorphimethine, with the unsatu-

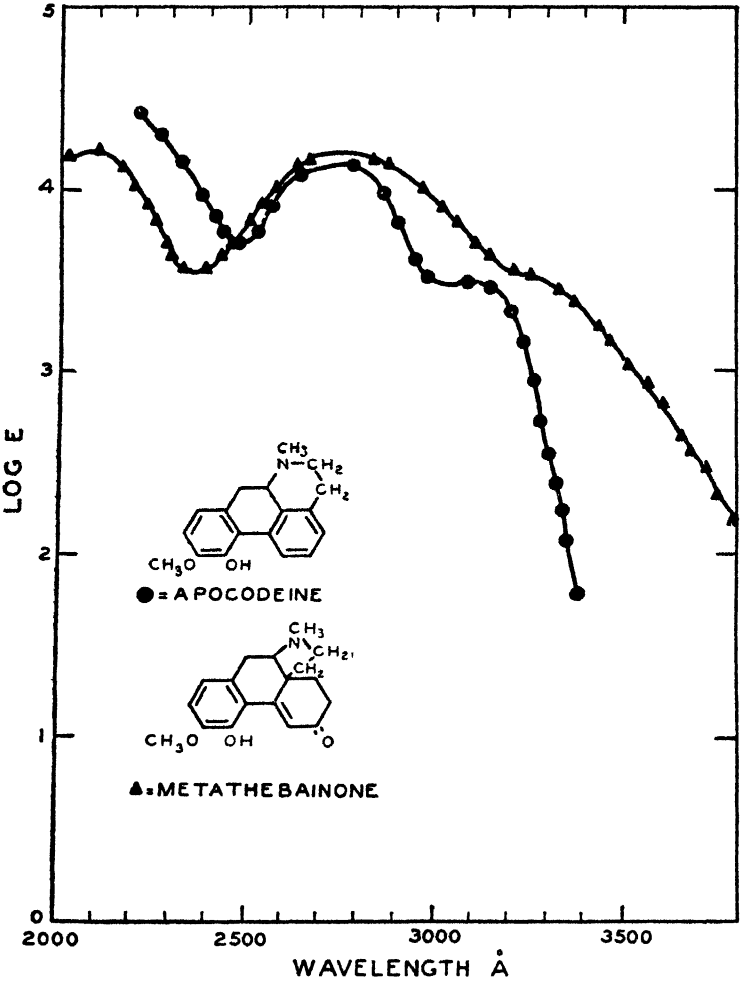


FIG. 9. ULTRAVIOLET ABSORPTION SPECTRA OF REARRANGEMENT TYPES, APOCODEINE AND METATHEBAINONE

ration of ring III out of conjugation, differs widely. Fig. 9 represents the spectra of two morphine types in which drastic rearrangement has taken place, apocodeine and metathebainone. We believe that the data of Fig. 8 strongly support the presence of the conjugated system of ring III, linked through the 9,10-double bond to the aromatic ring.

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[4] This compound can be converted by unequivocal methods to the well-known dihydrothebainone, which is further related through dihydrocodeinone to codeine.

A further attempt to answer the question of structural change was made by the biological method; if the products in question showed morphine- or thebaine-like action, this might be considered evidence of unchanged fundamental structure. The hydrochlorides of α-methyldihydrothebaine, (+) α-phenyldihydrothebaine, and norphenyldihydrothebaine, on subcutaneous injection into mice in the normal morphine dosage, showed practically no action, not even the Straub reaction. The evidence is thus negative, for we have found a number of morphine derivatives with the ether ring opened to be similarly inactive.

The structural question will be resumed in the methyldihydrothebaine series, where degradation to a known methylphenanthrene may be possible.

ACKNOWLEDGMENTS

We are indebted to Merck & Co., Rahway, for the large amount of thebaine used in this work; to the National Research Council (L.J.S.) and the Mallinckrodt Chemical Works (J.A.B.) for fellowship aid. Absorption spectra are by Peter Cole and Dorothy Peterson, x-ray diffraction patterns by William C. White and Dorothy Hastings, of the Laboratory of Physical Biology of this Institute. Biological tests are by Nathan B. Eddy. Microanalyses are from the Institute analytical service laboratory under the direction of C. A. Kinser. Optical crystallographic data for the phenyltetrahydrothebaimines are by George L. Keenan.

EXPERIMENTAL

(+) *α-Phenyldihydrothebaine* (II). As much ether as possible was distilled from 330 ml. of 2-molar phenylmagnesium bromide on the steam-bath, and 200 ml. of anhydrous benzene added. Under reflux, with mechanical stirring, 100 g. (0.5 molar equivalent) of thebaine in 1900 ml. of warm benzene was added during 2 hours. Refluxing and stirring was continued for 6 hours, and the solution was poured into excess saturated ammonium chloride solution. The aqueous layer was extracted several times with benzene, and the combined benzene extracts were shaken out with 2 *N* hydrochloric acid. The base was liberated with ammonia and brought into ether in the presence of a little sodium dithionite. The purple syrup left on removal of the ether was taken up in 150 ml. of absolute alcohol, and treated with alcoholic perchloric acid (55 g. of 60% aqueous perchloric acid in 120 g. of ice-cold absolute alcohol) to litmus acidity. The mixture of crystalline perchlorates was triturated with two 75-ml. portions of alcohol, which removed practically all color. Eight such runs gave 1102 g. of crude perchlorate (89%). Recovery from the mother liquors, passing through the base, not over 1%.

The crude perchlorate was converted (ether extraction) to the syrupy base, and this treated with alcoholic hydrogen chloride. After 12 hours at 0°, the colorless crystals of (+) α-phenyldihydrothebaine hydrochloride were washed with cold methanol. The mother liquors were concentrated, converted to base, and again to hydrochloride, thus removing practically all of the (+) α isomer; yield 75–78% (based on thebaine). The mother liquors contain the (+) δ isomer.

(+) α-Phenyldihydrothebaine is a glass-like solid; from cold alcoholic solution it slowly crystallizes solvated as colorless prisms, m.p. 40–70°, $(\alpha)_{D}^{20}$ +10.2° (alcohol, *c*, 1.98); satisfactory analyses on the solvated form could not be obtained.

Anal. Calc'd for $C_{25}H_{27}NO_3 + C_2H_5OH$: C, 74.4; H, 7.60; C_2H_5OH, 10.6.
Found: C, 72.2; H, 7.30; loss at 100°, 10.8.

The base distills at 150°/0.1 mm. as a colorless glass, which necessarily contains some of the (−) δ isomer; $(\alpha)_{D}^{20}$ +25.3° (alcohol, *c*, 0.75).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.1; H, 6.98.
Found: C, 77.1; H, 6.88.

The base is soluble in dilute alkali, precipitated by CO_2 or NH_4Cl; ferric chloride test negative, diazosulfanilic acid intense red; indifferent to catalytic hydrogenation in neutral solution.

(+) *α-Phenyldihydrothebaine perchlorate*, crystallized from alcohol, melts at 248° (vac., decomp.) and has $(\alpha)_{D}^{28}$ +35° (alcohol, *c*, 0.21); one gram dissolves in 65 ml. of boiling alcohol. It is more soluble in acetone, in which it has $(\alpha)_{D}^{20}$ +8.2° (*c*, 0.98).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.3; H, 6.03.

(+) *α-Phenyldihydrothebaine methiodide*, from methanol, melts at 216.5–218°; $(\alpha)_{D}^{28}$ +42.7° (alcohol, *c*, 0.36).

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.69.
Found: C, 58.9; H, 6.04.

Degradation of (+) *α-phenyldihydrothebaine.* A suspension of 307 g. of the methiodide in one liter of 30% aqueous KOH was boiled vigorously for 5 minutes. After cooling, the alkali was poured from the glassy solid (potassium salts of the degradation products), which was shaken with water and ether; hydrolysis was practically complete, but the aqueous layer was saturated with ammonium chloride and extracted again. At 3° overnight, the ether yielded 99 g. of (+) *α-phenyldihydrothebaine isomethine*; recovery from the filtrate brought the yield to 123 g. (52.8%).

The final liquor was concentrated to a syrup, dissolved in 150 ml. of alcohol, and treated with 270 ml. of 1 part alcohol in 1 part 10% aqueous perchloric acid. The first crop of fine white crystals separating immediately was the perchlorate of undegraded phenyldihydrothebaine, 41.3 g. (14%), $(\alpha)_D$ +4°, m.p. 223–230°; it was removed quickly to avoid contamination of the small crop of *phenyldihydrothebaine normal methine perchlorate* which crystallized soon after; 8.7 g. (3%), m.p. 93–122°, $(\alpha)_D$ −34°. The mother liquors, in ice, gave 24.4 g. (19%) of the more soluble isomethine perchlorate, m.p. 105–115°, $(\alpha)_D$ −127°; total yield of basic material, 89%.

(+) *α-Phenyldihydrothebaine isomethine* (XXI) was best purified as the perchlorate, from alcohol to constant rotation. The base liberated with ammonia was brought into ether and the resulting oil dissolved in warm 75% alcohol; crystallized at 0° twelve hours, and recrystallized from 75% alcohol, m.p. 101°, $(\alpha)_{D}^{20}$ −280° (alcohol, *c*, 2.73); alkali-soluble, ferric chloride negative, red dye with diazosulfanilic acid. Analyses showed it to be partially hydrated. It was distilled at 120°/0.1 mm.; $(\alpha)_{D}^{20}$ −280°.

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.2; H, 7.16.

The *perchlorate*, prepared in warm alcohol with 60% perchloric acid, crystallized in balls of needles, m.p. 111–117° (gas), $(\alpha)_{D}^{25}$ −197° (alcohol, *c*, 0.58; ethyl acetate, *c*, 1.21).

Anal. Calc'd for $C_{26}H_{30}ClNO_7 + C_2H_5OH$: C, 61.1; H, 6.60; C_2H_5OH, 8.4.
Found: C, 61.0; H, 6.99; loss at 100°, 7.3.

The *methiodide* crystallized hydrated from 25% alcohol as colorless, felted needles, m.p. 100–110°, $(\alpha)_{D}^{25}$ −207° (alcohol, *c*, 1.62).

Anal. Calc'd for $C_{27}H_{32}INO_3 + 2H_2O$: H_2O,. 6.2 Found: loss at 80°, 6.1.

The anhydrous salt melted at 159–160°, and appeared to become hydrated on short standing.

Anal. Calc'd for $C_{27}H_{32}INO_3 + 1.5H_2O$: C, 56.4; H, 6.49; H_2O, 4.7.
Found: C, 56.3; H, 6.64; loss, 5.5.

Cyclization. (+) *α-Phenyl-9-dimethylamino-6-methoxythebendiene* (XXI → XXVI). (+) α-Phenyldihydrothebaine isomethine was boiled for one minute with concentrated hydrochloric acid. The resulting oily product was insoluble in alkali, diazosulfanilic acid test negative. With 5% aqueous-alcoholic perchloric acid it gave a crystalline *perchlorate*, purified from alcohol, m.p. 168°; $(\alpha)^{22}_{D}$ +26.5° (alcohol, *c*, 0.11).

Anal. Calc'd for $C_{26}H_{30}ClNO_7$: C, 61.9; H, 6.00.
Found: C, 61.6; H, 6.36.

The *methiodide* formed long, square-ended prisms, m.p. 212–213°, $(\alpha)^{30}_{D}$ +0.6° (alcohol, *c*, 1.58).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.4; H, 5.91.
Found: C, 59.1; H, 6.21.

rac. Phenyl-6-methoxythebentriene (XXVII). The methiodide of the cyclized isomethine was degraded by boiling 3 minutes in 6% sodium ethoxide solution; dilution with water gave an amorphous solid, crystallized from ethyl acetate; m.p. 162.5–163°, $(\alpha)^{20}_{D}$ 0.0° (acetone, *c*, 0.48).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19; 2OCH$_3$, 17.3.
Found: C, 80.4; H, 6.16; OCH$_3$, 16.6.

XXVII was indifferent to acetylation, diazobenzene reaction negative; in ethyl acetate, blue-violet fluorescence.

rac. Phenyl-6-methoxythebendiene (XXVIII). In ethyl acetate with platinum oxide, XXVII absorbed one mole of hydrogen. The product crystallized from methanol in lustrous leaflets, m.p. 119–120.5, $(\alpha)^{20}_{D}$ 0.0° (ethyl acetate, *c*, 0.32).

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71.
Found: C, 79.8; H, 6.85.

rac. Phenyl-6-methoxythebenane (XXIX). The reduction of XXVII as above but with the addition of a little glacial acetic acid proceeded with the absorption of three moles of hydrogen; from acetone, long colorless prisms, m.p. 80–83.5°, $(\alpha)^{20}_{D}$ 0.0° (ethyl acetate, *c*, 0.37).

Anal. Calc'd for $C_{24}H_{28}O_3$: C, 79.1; H, 7.74.
Found: C, 79.0; H, 8.19.

DEGRADATION OF (+) α-PHENYLDIHYDROTHEBAINE ISOMETHINE

(+) *Vinylphenyldihydrothebaol* (XIX). (+) α-Phenyldihydrothebaine isomethine methiodide was refluxed with 6% sodium ethoxide solution for one hour. Dilution with water precipitated a granular product, which was suspended in ether and washed with dilute HCl. The residue from ether was crystallized from alcohol, 78% yield; m.p. 149°, $(\alpha)^{25}_{D}$ +47.1° (ethyl acetate, *c*, 0.51).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19; 2 OCH$_3$, 17.3.
Found: C, 80.5; H, 6.43; OCH$_3$, 17.3.

XIX couples with diazotized aniline in alcoholic alkali to give an orange-red dye.

Degradation with 30% aqueous KOH gave only 33% yield, and apparently caused some racemization, $(\alpha)^{20}_{D}$ +21.4°. XIX also shows lowered rotation after heating with KOH.

(+) *Acetylvinylphenyldihydrothebaol.* In pyridine with acetic anhydride for 50 hours, XIX gave an acetyl derivative, colorless quadratic plates from alcohol, m.p. 145.5–147°; $(\alpha)^{22}_{D}$ +24.7° (ethyl acetate, *c*, 0.32).

Anal. Calc'd for $C_{26}H_{24}O_4$: C, 78.0; H, 6.04.
Found: C, 77.7; H, 5.91.

(+) *Ethylphenyldihydrothebaol* (XVIII). Three grams of XIX in neutral ethyl acetate with 100 mg. of platinum oxide absorbed 246 ml. of hydrogen (for 1 mole, 210 ml.). The crystalline product from evaporation was purified from alcohol, 2.6 g., m.p. 118°, $(\alpha)^{25}_{D}$ −74.4° (ethyl acetate, *c*, 0.31); mixed m.p. with product from degradation of XXII, 118°.

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71.
Found: C, 79.6; H, 6.76.

Its *acetyl derivative* crystallized from ethanol in rectangular plates, m.p. 122.5–123°, $(\alpha)^{25}_{D}$ −77.0° (ethyl acetate, *c*, 0.31); mixed m.p. with acetyl degraded XXII, 122.5–123°.

Anal. Calc'd for $C_{26}H_{26}O_4$: C, 77.6; H, 6.51.
Found: C, 77.6; H, 6.63.

(+) *Ethylphenylhexahydrothebaol* (XVII). When the hydrogenation of XIX was carried out as above but with addition of a little gl. acetic acid, two moles of hydrogen were taken up in 15 minutes, and a third in 36 hours. The product was an oil, whose acetyl derivative crystallized from 70% alcohol, m.p. 82.5–83° $(\alpha)^{20}_{D}$ −23.4° (ethyl acetate, *c*, 0.26).

Anal. Calc'd for $C_{26}H_{30}O_4$: C, 76.8; H, 7.44.
Found: C, 76.4, 77.3; H, 7.10, 7.21.

Cyclization of (+) *vinylphenyldihydrothebaol to rac. phenyl-6-methoxythebentriene* (XIX → XXVII). (+) Vinylphenyldihydrothebaol was boiled for 10 minutes in conc'd HCl and dioxane (10:1). Dilution with water precipitated a strongly phenolic resin, which after distillation in a high vacuum showed $(\alpha)^{20}_{D}$ −115° (acetone, *c*, 1.09). This was methylated in alkali with dimethyl sulfate, giving an amorphous, non-phenolic product having $(\alpha)^{20}_{D}$ −111° (acetone, *c*, 0.48). This was racemized by boiling with sodium ethoxide solution for ten minutes, and crystallized from ethyl acetate; m.p. 161–163°, no depression in mixture with *rac.* phenyl-6-methoxythebentriene (XXVII) from degradation of XXVI; $(\alpha)^{26}_{D}$ 0.0° (acetone, *c*, 0.96).

(+) *α-Phenyldihydrothebaine dihydroisomethine* (XXII). A solution of 11.5 g. of the isomethine in 300 ml. of alcohol with 50 mg. of platinum oxide absorbed one mole of hydrogen in 30 min. The colorless solution rapidly took on a yellow-green fluorescence in contact with air. Alcohol was removed to 75 ml., and 60% $HClO_4$ added until the fluorescence disappeared (Congo acidity). On addition of 50 ml. of ether, 13.2 g. of fine white needles separated. The base was liberated with ammonia, brought into ether, and the residue from the ether was purified from 70% alcohol, m.p. 70–72°, $(\alpha)^{20}_{D}$ −175° (alcohol, *c*, 1.06).

Anal. Calc'd for $C_{26}H_{31}NO_3$: C, 77.0; H, 7.71.
Found: C, 76.7; H, 7.97.

The *perchlorate* crystallized solvated from 25% alcohol, m.p. 85–87° (foaming) and showed in alcohol $(\alpha)^{25}_{D}$ −104° (*c*, 1.08). It lost 8.7% in a vacuum at 57° and then had the m.p. 111–117°; calc'd for $3H_2O$: 9.6, for C_2H_5OH: 8.2. When brought to analysis it again melted at 85° and appeared to be the dihydrate.

Anal. Calc'd for $C_{26}H_{32}ClNO_7 + 2H_2O$: C, 57.6: H, 6.64; H_2O, 6.6.
Found: C, 57.7, 57.6; H, 7.05, 6.79; loss at 110°, 6.5.

The *methiodide* was prepared in ethyl acetate, purified from dilute methanol; m.p. 212–213°, $(\alpha)^{25}_{D}$ −121° (alcohol, *c*, 2.86).

Anal. Calc'd for $C_{27}H_{34}INO_3 + 1.5\ H_2O$: C, 56.4; H, 6.49, I, 22.1; H_2O, 4.7.
Found: C, 56.8, 56.3; H, 6.49, 6.64; I, 22.1; loss at 110°, 5.9.

Degradation of this methiodide by boiling for 90 min. with 6% sodium ethoxide solution gave ethylphenyldihydrothebaol (XVIII) of m.p. 118°, $(\alpha)^{20}_{D}$ −76.7° (ethyl acetate, *c*, 0.36); mixed m.p. with product from hydrogenation of XIX, 118°.

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71; 2 OCH_3, 17.2.
Found: C, 80.0; H, 6.77; OCH_3, 17.3.

Acetylation in pyridine gave sparkling rectangular plates (from alcohol) of m.p. 122.5–123°, mixed m.p. with acetyldihydro-XIX, 122.5–123°, $(\alpha)^{20}_{D}$ −77.8° (ethyl acetate, *c*, 0.32).

Anal. Calc'd for $C_{26}H_{26}O_4$: C, 77.6; H, 6.51.
Found: C, 77.5; H, 6.56.

(+) *α-Hexahydrophenyldihydrothebaine dihydroisomethine.* Three grams of pure (+) α-isomethine (XXI) in 50 ml. of alcohol with 50 ml. of *N* hydrochloric acid and 400 mg. of platinum oxide absorbed 917 ml. of hydrogen (calc'd for 4 moles, 848 ml.). Removal of alcohol and isolation with ammonia and ether gave long white needles (from 75% alcohol), m.p. 108–108.5°, $(\alpha)^{20}_{D}$ −24.2° (alcohol, *c*, 1.78); brilliant yellow-green fluorescence in alcoholic solution.

Anal. Calc'd for $C_{26}H_{37}NO_3$: C, 75.8; H, 9.06.
Found: C, 75.7; H, 9.21.

The *methiodide* from methanol had m.p. 207–208°, $(\alpha)_D^{20}$ −14.7° (alcohol, *c*, 1.16).

Anal. Calc'd for $C_{27}H_{40}INO_3$: I, 22.9. Found: I, 22.9.

This salt is isomeric with the N-methomethiodides of (+) and (−) hexahydrophenyltetrahydrothebaimines.

(+) *α-Phenyldihydrothebaine methine* (VI). The normal methine, isolated as described under the degradation of (+) α-phenyldihydrothebaine, was purified as perchlorate, and recrystallized as base from 75% methanol; m.p. 126–127°, $(\alpha)_D^{20}$ −46.5° (alcohol, *c*, 0.86).

Anal. Calc'd for $C_{26}H_{29}NO_4$: C, 77.4; H, 7.25.
Found: C, 77.7; H, 7.45.

The *perchlorate* crystallized solvated from ethanol, melting range 106–120° (gas evolution), and had $(\alpha)_D^{20}$ −60.3° (alcohol, *c*, 0.26), $(\alpha)_D^{20}$ −34° (acetone, *c*, 1.12).

Anal. Calc'd for $C_{26}H_{30}ClNO_7 + C_2H_5OH$: C, 61.1; H, 6.60; C_2H_5OH, 8.4.
Found: C, 60.8; H, 6.81; loss at 110°, 8.0.

The *methiodide* was prepared in ethyl acetate and purified from methanol, m.p. 244° (evac. tube), $(\alpha)_D^{20}$ −51.5° (alcohol, *c*, 0.41).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.4; H, 5.91.
Found: C, 59.4; H, 6.18.

The normal methine is soluble in alkali, and couples to a red dye with diazosulfanilic acid. It is unaffected by boiling with concentrated HCl (recovery 95%), in contrast to the isomethine. For hydrogenation, see under (+) phenyltetrahydrothebaimine.

rac. Vinylphenyldihydrothebaol (XXIV). (+) α-Phenyldihydrothebaine methine is so resistant to degradation that boiling the methiodide with 40% KOH gives only the methohydroxide, long, yellow, felted needles. Distillation of this in the oil-pump vacuum at 160° gave *rac.* vinylphenyldihydrothebaol, m.p. 149.5°, $(\alpha)_D^{20}$ 0.0° (ethyl acetate, *c*, 0.39), identical with the racemate (?) obtained by combination of the (+) and (−) isomers [see degradation of (−) δ-phenyldihydrothebaine].

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19; 2 OCH_3, 17.3.
Found: C, 80.5; H, 6.48; OCH_3, 17.1.

(+) *δ-Phenyldihydrothebaine* (III). The alcoholic mother liquor from preparation of (+) α-phenyldihydrothebaine hydrochloride (*ex* 100 g. of thebaine) was concentrated at 40° *in vacuo* to a heavy syrup; this was dissolved in 100 ml. of water, base liberated with ammonia, and taken into ether. The residue from the ether crystallized on dilution with a little alcohol, yield 9.8 g. (7.8% based on thebaine), pale lavender, m. *ca.* 140°; crystallized twice from abs. alcohol, white needles, m.p. 143.5°, $(\alpha)_D^{20}$ −110° (U.S.P. $CHCl_3$, *c*, 1.10); $(\alpha)_D^{20}$ −131° (*c*, 0.87, acetone). Occasionally the color was persistent, but could be removed by passing through the hydrochloride (3*N* HCl and sat'd NH_4Cl).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.1; H, 6.98.
Found: C, 76.9; H, 7.15.

The *perchlorate*, prepared in alcohol with 20% alcoholic perchloric acid, was much more soluble than that of the (+) α isomer, 1 g. in 18 ml. of boiling alcohol; purified from alcohol-ether, m.p. 209–213°, $(\alpha)_D^{24}$ −44.5° (alcohol, *c*, 1.23).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.4; H, 5.92.

The *methiodide* was prepared in ethyl acetate, purified from methanol, m.p. 206–208°, $(\alpha)_D^{23}$ −43° (alcohol, *c*, 0.72). It was solvated, calc'd for CH_3OH: 5.7; for $2H_2O$: 6.3. Loss at 100°: 5.8.

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.68.
Found: C, 58.6; H, 5.92.

(+) *δ-Phenyldihydrothebaine isomethine* (IX). (+) δ-Phenyldihydrothebaine methiodide was boiled for 15 min. with 30% aqueous KOH, the potassium salt of the product hydrolyzed with ammonium chloride, and extracted with ether. The ether residue crystallized from 70% alcohol in long prisms, m.p. 117–119°, $(\alpha)_D^{25}$ +153° (alcohol, c, 0.63); yield 70%. It sublimed in long, feathery crystals at 140°/0.1 mm., m.p. unchanged.

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.4, 77.1; H, 7.75, 7.10.

The *perchlorate* was prepared in alcohol with 20% alcoholic perchloric acid, purified from abs. alcohol; solvated, m.p. 114–116°, $(\alpha)_D^{23}$ +89.6° (alcohol, *c*, 0.67).

Anal. Calc'd for $C_{28}H_{30}ClNO_7 + 2C_2H_5OH$: C, 60.4; H, 7.10; C_2H_5OH, 15.5.
Found: C, 60.3; H, 6.81; loss at 100°, 15.5.

The *methiodide*, prepared in ethyl acetate and purified from abs. alcohol-ether, had the m.p. 202–203°, $(\alpha)_D^{24}$ +108° (alcohol, *c*, 0.99).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.5; H, 5.91.
Found: C, 59.7; H, 6.17.

Degradation of (+) *δ-phenyldihydrothebaine isomethine.* Treatment of the methiodide of IX with boiling sodium ethoxide yielded (+) vinylphenyldihydrothebaol (XIX), identical with that from the parallel degradation of the (+) α-isomethine (XXI). It showed $(\alpha)_D^{24}$ +46.6° (ethyl acetate, *c*, 0.58), m.p. 149°, mixed m.p. 149°.

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19.
Found: C, 80.8; H, 6.14.

(+) *δ-Phenyldihydrothebaine dihydroisomethine* (X). The (+) δ-isomethine (IX) in dilute acetic acid with platinum oxide took up one mole of hydrogen rapidly. The product was liquid, and was converted to the methiodide, purified from alcohol-ether; m.p. 217–219° (gas), $(\alpha)_D^{23}$ +145° (alcohol, *c*, 0.32).

Anal. Calc'd for $C_{27}H_{34}INO_3$: I, 23.2. Found: I, 22.9.

Degradation of the methiodide with sodium ethoxide solution gave 50% yield of (+) ethylphenyldihydrothebaol (XVIII), identical with that from the (+) α-dihydroisomethine (XXII). It showed $(\alpha)_D^{23}$ −76.0° (ethyl acetate, *c*, 0.27), m.p. 118°, mixed m.p. 118°; sublimed for analysis.

Anal. Calc'd for $C_{24}H_{24}O_3$: C, 80.0; H, 6.71.
Found: C, 80.2; H, 6.75.

Cyclization and degradation of (+) *δ-isomethine* (IX → XXVII). A solution of the (+) δ-isomethine (IX) in conc'd HCl was boiled for five minutes, treated with NaOH, and the oily, non-phenolic product converted to the methiodide, m.p. 170–173°, $(\alpha)_D^{28}$ −3.8° (alcohol, *c*, 1.05). [Compare properties of the isomer drived from XXVI in the (+) α-series.] Degradation with boiling sodium ethoxide eliminated the isomerism; the N-free end-product was identical with *rac.* phenyl-6-methoxythebentriene (XXVII), m.p. and mixed m.p. 161–162°, $(\alpha)_D^{25}$ 0.0° (acetone, *c*, 0.38).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19.
Found: C, 80.3; H, 6.25.

(−) *δ-Phenyldihydrothebaine* (IV). Solvent free (+) α-phenyldihydrothebaine (168 g.) was sealed in an evacuated flask and held at 200° ± 2° for 80 hours. The fluorescent yellow resin, while still warm, was brought into 250 ml. of alcohol, seeded with a sample from a sample from a small test run, and held at 3° for 2 days. The crystals were washed white with cold alcohol, m.p. 138–140°, 27 g. (16%); recrystallized twice from abs. alcohol, white needles, m.p. 143.5°, $(\alpha)_D^{20}$ +110° (U.S.P. $CHCl_3$, *c*, 1.10); $(\alpha)_D^{20}$ +131° (acetone, *c*, 0.66).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.1; H, 6.99.
Found: C, 76.9; H, 7.29.

The base is alkali-soluble; gives no ferric chloride test, but forms a brilliant red dye with diazosulfanilic acid; indifferent to catalytic hydrogenation in neutral solution.

From the alcoholic mother liquor (+) α-phenyldihydrothebaine was recovered as perchlorate in 70% of the possible yield.

(−) *δ-Phenyldihydrothebaine perchlorate* was prepared in, and purified from alcohol, m.p. 209–213°, $(\alpha)_D^{24}$ +42.8° (alcohol, *c*, 0.63).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.
Found: C, 61.2; H, 6.09.

The *methiodide*, like its optical opposite, crystallized solvated from methanol (calc'd for CH_3OH: 5.7; for $2H_2O$: 6.3; found: loss at 100° 6.3). It had m.p. 206–208°, $(\alpha)_D^{20}$ +44° (alcohol, *c*, 0.32).

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.69.
Found: C, 58.8; H, 6.00.

(−) *δ-Phenyldihydrothebaine isomethine* (XXX). The methiodide of IV was degraded in 98% yield by boiling for 5 minutes with 30% KOH. The viscous potassium salt was hydrolyzed with ammonium chloride and extracted with ether, which left long leaflets. It was purified as perchlorate, regenerated, and crystallized from 60% alcohol; m.p.-117–119°, $(\alpha)_D^{20}$ −154° (alcohol, *c*, 0.92). It sublimed at 140°/0.1 mm. in long feathery crystals.

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.

Found: C, 77.2; H, 7.59.

The perchlorate crystallized from abs. alcohol solvated, m.p. 114–116°, $(\alpha)_D^{20}$ −90° (alcohol, *c*, 0.69). The solvent-free salt could not be brought to satisfactory analytical purity.

Anal. Calc'd for $C_{26}H_{30}ClNO_7$: C, 61.9; H, 6.00.

Found: C, 61.2; H, 6.06.

The methiodide, purified from abs. alcohol-ether melted at 202–203°, $(\alpha)_D^{25}$ −105° (alcohol, *c*, 0.40).

Anal. Calc'd for $C_{27}H_{32}INO_3$: C, 59.4; H, 5.91.

Found: C, 59.4; H, 5.80.

(−) *Vinylphenyldihydrothebaol* (XXIII). The (−) δ-isomethine methiodide was degraded like its (+) analog, and the product purified from alcohol; m.p. 149.5–150°, $(\alpha)_D^{22}$ −47.4° (ethyl acetate, *c*, 0.17).

Anal. Calc'd for $C_{24}H_{22}O_3$: C, 80.4; H, 6.19.

Found: C, 80.2; H, 6.07.

Equal amounts of this compound and the (+) analog (XIX) were mixed and crystallized from alcohol. The product had $(\alpha)_D^{20}$ 0.0° (ethyl acetate, *c*, 0.21), m.p. 146–147°, and is probably identical with the racemic compound (XXIV) from degradation of the (+) α normal methine; mixed m.p. 146–147°.

Conversion of (−) *δ-phenyldihydrothebaine to* (+) *α-phenyldihydrothebaine* IV → II. Three grams of pure IV in a sealed tube under oil-pump vacuum was held at 200° ± 4° for 60 hrs. The product was a dark glass, in contrast to the reverse transformation, II → IV; this perhaps resulted from the inadvertant use of a soft-glass tube. It was taken up in 8 ml. of hot abs. alcohol and seeded with IV; a small amount crystallized but could not be purified enough for positive identification.

The dark mother liquor was acidified with 60% perchloric acid; brown crystals, 2.2 g. (59%). It was digested with carbon in 125 ml. of alcohol, large glassy colorless crystals; analytical sample by two more crystallizations; m.p. 248° (vac., dec.), $(\alpha)_D^{20}$ +37° (alcohol, *c*, 0.209).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.

Found: C, 61.3; H, 5.93.

Further identification by x-ray diffraction pattern (Fig. 1).

(−) *α-Phenyldihydrothebaine* (V). Pure (+) δ-Phenyldihydrothebaine (7.6 g.) in a sealed tube under a high vacuum was heated at 200° ± 2° for 50 hours. The pale yellow glassy product was dissolved in 10 ml. of abs. alcohol and seeded with the (+) δ-isomer. After 12 hours at 0°, the crystals were washed with 5 ml. of cold alcohol; recovery 1.8 g. (23%), m.p. 138°.

The mother liquor was brought to acidity with 60% perchloric acid, and the crystals washed with 20 ml. of cold alcohol, pure white, 6.7 g. (74%). The salt was purified from alcohol, solubility boiling 1 g./65 ml. like the (+) α-salt; m.p. 248° (vac., dec.), $(\alpha)_D^{20}$ −8.0° (acetone, *c*, 1.25), $(\alpha)_D^{20}$ −35° (alcohol, *c*, 0.20).

Anal. Calc'd for $C_{25}H_{28}ClNO_7$: C, 61.3; H, 5.76.

Found: C, 61.1; H, 5.96.

The base liberated from the salt was a colorless glass like its optical opposite; $(\alpha)_D^{20}$ −10° (alcohol, *c*, 0.22). No attempt was made to prepare the crystalline solvated form, whose indefinite properties make it worthless for identification.

The methiodide was purified from methanol, m.p. 216°, $(\alpha)_D^{25}$ −43.6° (alcohol, *c*, 0.27).

Anal. Calc'd for $C_{26}H_{30}INO_3$: C, 58.8; H, 5.69.

Found: C, 60.0; H, 6.06.

(−) *α-Phenyldihydrothebaine isomethine.* A suspension of 2.4 g. of (−) α-methiodide in 10 ml. of 30% KOH was boiled 5 min. The separated resin was treated with ether and dilute ammonium chloride. The residue from the ether, in 5 ml. of hot alcohol was made acid to Congo with 10% aqueous $HClO_4$; yield of solvated, white salt, 2.3 g. (95%). It was recrystallized from 7 ml. of alcohol, filtering from 150 mg. of undegraded (−) α-phenyldihydrothebaine perchlorate, $(\alpha)^{20}_{D}$ −35.5°. The crystals from the filtrate melted at 112–118°, gas evol., but probably contained some of the normal methine salt, for $(\alpha)^{20}_{D}$ was +168°. It was fractionated from alcohol to free it of the more soluble normal methine, and yielded the pure isomethine perchlorate, m.p. 111–116°, $(\alpha)^{20}_{D}$ +197° (alcohol, *c*, 0.61). At 100°/0.1 mm. it lost 6.6%, calc'd for C_2H_5OH, 8.4%.

Anal. Calc'd for $C_{26}H_{30}ClNO_7$: C, 62.0; H, 6.00.
Found: C, 61.9; H, 6.18.

The base liberated from the perchlorate was crystallized from 75% alcohol, m.p. 101°, $(\alpha)^{20}_{D}$ +281° (alcohol, *c*, 1.12).

Anal. Calc'd for $C_{26}H_{29}NO_3$: C, 77.4; H, 7.25.
Found: C, 77.1; H, 7.33.

(+) *Phenyltetrahydrothebaimine* (VIII). Thirty grams of (+) α-phenyldihydrothebaine (II) in 220 ml. of *N* acetic acid with 20 ml. of 5% gum arabic solution and 60 ml. of palladous chloride solution (1% Pd) absorbed 1 mole (1750 ml.) of hydrogen in 20 minutes and stopped abruptly. The catalyst-free solution was washed with ether, and the base liberated with ammonia in the presence of a trace of sodium dithionite, and extracted with ether. The product was purified from ethyl acetate, and 75% alcohol; yield 23 g. (85%), pentagonal plates (Fig. 3). It had the m.p. 120–121°, $(\alpha)^{20}_{D}$ −35.0° (acetone, *c*, 1.14), $(\alpha)^{20}_{D}$ −4.2° (10% acetic acid, *c*, 1.19). It gave no ferric chloride test, but was soluble in alkali, and gave a red dye with diazosulfanilic acid. x-Ray diffraction pattern, Fig. 6.

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.3; H, 7.66.

The reduction of (+) δ-phenyldihydrothebaine was carried out similarly, except that 18 hours was required. The product was identical with that described above, m.p. and mixed m.p. 121°, $(\alpha)^{20}_{D}$ −32.7° (acetone, *c*, 2.63).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.7; H, 7.30.

(+) *Phenyltetrahydrothebaimine N-methomethiodide* (VII). When VIII was warmed in benzene with methyl iodide, white crystals of the N-methomethiodide separated in 46% yield, the remainder staying in solution as the secondary base hydriodide (from which VIII could be recovered). VII melted at 235° (evac. tube) and was dimorphous; after grinding gently, m.p. 250–253°; $(\alpha)^{24}_{D}$ −5.2° (*c*, 2.67, methanol), $(\alpha)^{24}_{D}$ −3.3° (*c*, 2.11, ethanol).

Anal. Calc'd for $C_{27}H_{34}INO_3$: C, 59.2; H, 6.26.
Found: C, 59.2; H, 6.71.

(+) Phenyltetrahydrothebaimine derived from the (+) δ-isomer gave the same dimorphous N-methomethiodide, m.p. 235° and 250–254°, $(\alpha)^{25}_{D}$ −5.8° (*c*, 1.21 methanol), $(\alpha)^{25}_{D}$ −3.5° (*c*, 1.73, ethanol); mixed m.p., because of the grinding, 250–254°.

(+) α-Phenyldihydrothebaine normal methine (VI) was hydrogenated (one mole) in ethanol with platinum oxide, and the oily dihydromethine (XII) converted to the methiodide, yield quantitative. It was identical with the two N-methomethiodides described above, m.p. 235° and 251–254°, no depression in mixture with either; $(\alpha)^{25}_{D}$ −5.4° (*c*, 3.30 methanol), −3.9° (*c*, 2.85, ethanol).

Anal. Calc'd for $C_{27}H_{34}INO_3$: C, 59.2; H, 6.26.
Found: C, 59.1; H, 6.79.

(−) *Phenyltetrahydrothebaimine* (XII). (−) δ-Phenyldihydrothebaine (IV), 5 g., m.p. 142°, absorbed 1 mole of hydrogen in 4 hours under the conditions described for reduction of the (+) α and (+) δ compounds (II and III). The product was isolated and purified essentially as above, giving 4.5 g. of faintly pink (colloidal palladium) pentagonal plates (Fig. 4) of m.p. 121°, $(\alpha)^{20}_{D}$ +35.5° (acetone, *c*, 1.01). The color could be removed by sublimation *in vacuo* at 150°, needle clusters, m.p. 121°, $(\alpha)^{20}_{D}$ +35.4°.

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7: H, 7.47.
Found: C, 76.5, H, 7.88.

The N-methomethiodide melted at 235° (evac. tube) and had $(\alpha)^{20}_{D}$ +5.3° (methanol, *c*, 2.31).

Anal. Calc'd for $C_{27}H_{34}INO_3$: C, 59.2: H, 6.26.
Found: C, 59.1; H, 6.05.

The high-melting dimorphous form of this compound corresponding to that described in the (+) series (prepared seven years earlier and in a different Laboratory) could not be obtained, nor (lacking seed) was it possible to repeat the transformation with samples of the (+) compounds.

XIII from (−) α-phenyldihydrothebaine. The amorphous base was liberated from 2 g. of pure V perchlorate, and reduced in dilute acetic acid as described for the other isomers. One mole of hydrogen (122 ml., 28°) was absorbed in 2.5 hours. The purple (colloidal Pd) solution was decolorized, saturated with ether, and the base precipitated crystalline with ammonia (seeding with XIII obtained from reduction of IV, above); 1.5 g. (94%). It was purified from ethyl acetate, m.p. and mixed m.p. 120.5–121°. Sublimed for analysis, $(\alpha)^{20}_{D}$ +35.5° (acetone, *c*, 1.00); +4.9° (10% acetic acid, *c*, 1.02).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.6; H, 7.35.

rac. Phenyltetrahydrothebaimine (XIV). Equal amounts of the imines from the (+) *α* and (−) *δ* series were dissolved in boiling alcohol; in several attempts mixed crystals of m p. 105–108° were obtained. Through unknown factors, the racemate suddenly crystallized from the hot solution in long crystal bundles (Fig. 5) of m.p. 134°, $(\alpha)^{20}_{D}$ 0.0° (acetone, *c*, 0.6).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.7; H, 7.47.
Found: C, 76.7; H, 7.82.

The imines from the (+) *δ*, (−) *α*, the (+) *δ*, (−) *δ*, and (+) *α*, (−) *α* series were pairwise dissolved in boiling alcohol and seeded with the above racemate; crystals separated immediately from the boiling solution. These three racemates were identical with that above, m.p. 134°, $(\alpha)^{20}_{D}$ 0.0° ± 0.1° (acetone, *c*, 0.5, 0.8, 0.8). The four racemates were mixed in the six possible combinations, and showed in each the sharp m.p. 134°.

CRYSTALLOGRAPHIC EXAMINATION

The optical crystalline properties of the (+), (−), and racemic phenyltetrahydrothebaimines were determined by Dr. Geo. L. Keenan.

"*(+) Phenyltetrahydrothebaimine.* Appearance in Ordinary Light: The significant habit is thin plates, five-sided in outline and usually referred to as uniterminal or hemimorphic.

Characters Shown in Parallel Polarized Light (crossed nicols): The elongated forms show parallel extinction. The polarization colors are brilliant and striking. The hemimorphic plates usually extinguish sharply and many irregular fragments remain bright when the microscope stage is revolved with nicols crossed.

Characters Shown in Convergent Polarized Light (crossed nicols): The substance is biaxial and optic axis figures are commonly shown with positive optic sign.

Refractive Indices: The significant refractive indices are: α = 1.568, β = 1.630, γ = 1.698; all ± 0.002. The α and β values are most commonly found on the substance.

As would be expected, the physical isomer, (−) *phenyltetrahydrothebaimine*, has identical optical crystallographic properties as those described above."

"*Racemic (+−) Phenyltetrahydrothebaimine.* Appearance in Ordinary Light: The significant habit is rod-shaped, some of the elongated forms breaking up into irregular fragments when powdered for microscopic examination. Many of the elongated forms also have blunt, spear-shaped terminations, others square ends.

Characters Shown in Parallel Polarized Light (crossed nicols): The extinction is parallel and the sign of elongation is negative. With crossed nicols, many of the elongated forms are observed to be thin, showing low order whites, the thicker rods exhibiting more brilliant polarization colors.

Characters Shown in Convergent Polarized Light (crossed nicols): The substance is biaxial, the interference figure showing the plane of the optic axes, with positive optic sign. The axial angle (2 E) is quite small, the interval between the melatopes being readily observed within the microscopic field.

Refractive Indices: The significant refractive indices are: $\alpha = 1.638$, $\beta = 1.640$, $\gamma = 1.698$; all ± 0.002. The α value is usually shown lengthwise on elongated forms and the β value crosswise.

The racemate, therefore, is distinctly different microscopically from the isomers already described."

(+) *Hexahydrophenyltetrahydrothebaimine* (XVI). Six grams of (+) α-phenyldihydrothebaine in 50 ml. of alcohol with 100 ml. of *N* hydrochloric acid absorbed four moles of hydrogen in 50 hours (platinum oxide). The product was isolated in the usual way and purified from ethyl acetate, yield nearly quantitative; slender, colorless prisms, m.p. 129–130.5°, $(\alpha)^{28}_{D}$ −8.5° (alcohol, *c*, 0.73). Analysis showed partial hydration, so it was sublimed in the oil-pump vacuum, 140°.

Anal. Calc'd for $C_{25}H_{35}NO_3$: C, 75.4; H, 8.90.

Found: C, 75.4; H, 9.05.

The same product was obtained by hydrogenation of (+) δ-phenyldihydrothebaine under these conditions, absorption 4 moles, yield quantitative; m.p. and mixed m.p. 129–130.5°, $(\alpha)^{25}_{D}$ −9° (alcohol, *c*, 1.0).

The *hydrochloride* crystallized from ethanol-ether in slender prisms, m.p. 253–255° (gas evol.), $(\alpha)^{28}_{D}$ −17.6° (alcohol, *c*, 0.25).

Anal. Calc'd for $C_{25}H_{36}ClNO_3$: C, 69.2; H, 8.36.

Found: C, 69.3; H, 8.24.

Reduction of (+) phenyltetrahydrothebaimine derived from either (+) α- or (+) δ-phenyldihydrothebaine, absorption 3 moles, yielded the same substance, m.p. and mixed m.p. 129–130.5°, $(\alpha)^{25}_{D}$ −9.0° (alcohol, *c*, 1.0).

N-methomethiodide. (+) Hexahydrophenyltetrahydrothebaimines from the four sources described gave identical N-methomethiodides (in benzene), yield 41%; m.p. 231–232.5°, $(\alpha)^{28}_{D}$ −4.8° (alcohol, *c*, 0.31).

Anal. Calc'd for $C_{27}H_{40}INO_3$: C, 58.6; H, 7.38; I, 22.9.

Found: C, 58.5: H, 7.33; I, 22.9.

The benzene mother liquor contained the hydriodide of the unchanged secondary base, which was recovered in 46% yield.

(+) *Vinylhexahydrophenyltetrahydrothebaol* (XX). This was obtained by sodium ethoxide degradation of the N-methomethiodides of XVI derived from both the (+) α and (+) δ series; colorless needles from 75% alcohol, m.p. 75.5–77°, $(\alpha)^{29}_{D}$ −22.7° (ethyl acetate, *c*, 0.33).

Anal. Calc'd for $C_{24}H_{30}O_3 + 1/4H_2O$: C, 77.7; H, 8.39; 2 OCH_3, 16.7; H_2O 1.2.

Found: C, 77.8; H, 8.50; OCH_3, 16.7; loss at 100° 0.7.

It was sublimed at 140°/0.1mm.

Anal. Calc'd for $C_{24}H_{30}O_3$: C, 78.7; H, 8.25.

Found: C, 78.6; H, 8.69.

It coupled with diazotized aniline to give an orange-red dye; it also formed an acetyl derivative of m.p. 79–80.5° and $(\alpha)^{28}_{D}$ −26.6° (ethyl acetate, *c*, 0.23).

(−) *Hexahydrophenyltetrahydrothebaimine* (XXXI) was prepared by reduction of (−) δ-phenyldihydrothebaine (4 moles of hydrogen) in the same manner as the optical opposite. The product had m.p. 128–129.5°, $(\alpha)^{25}_{D}$ +10.0° (alcohol, *c*, 0.90). The *N-methomethiodide* had m.p. 231–232°, $(\alpha)^{25}_{D}$ +6.6° (alcohol, *c*, 0.60). It gave on degradation (−) *vinylhexahydrophenyltetrahydrothebaol* (XXXII), m.p. 70–75°, $(\alpha)^{26}_{D}$ +35.4°; which could not be brought to analytical purity because of scarcity.

(+) *Vinylphenyltetrahydrothebaol* (XI). Degradation of (+) phenyltetrahydrothebaimine N-methomethiodide (VII) with sodium ethoxide solution gave 72% yield of N-free product, crystallized from 75% alcohol, m.p. 85.5–87°, $(\alpha)_D^{30}$ −58.7° (alcohol, *c*, 0.43). Acetylation in pyridine gave the *acetyl derivative*, rectangular prisms from methanol, m.p. 102–104°, $(\alpha)_D^{28}$ −48.5° (ethyl acetate, *c*, 0.27).

Anal. Calc'd for $C_{26}H_{26}O_4$: C, 77.6; H, 6.51; 2 OCH_3, 15.4.
Found: C, 77.7; H, 6.84; OCH_3, 15.6.

On reduction (platinum oxide) of this in ethyl acetate containing acetic acid, two moles of hydrogen were absorbed, giving *acetylethylphenylhexahydrothebaol*, m.p. 80°, alone or in mixture with the product obtained from (+) α-phenyldihydrothebaine isomethine (XXI → XIX → XVIII → XVII); $(\alpha)_D^{25}$ −29° (ethyl acetate, *c*, 0.31).

Norphenyldihydrothebaine. A solution of 12 g. of (+) α-phenyldihydrothebaine in 40 ml. of 48% hydrobromic acid was refluxed for 30 min. The hydrobromide of norphenyldihydrothebaine separated on cooling, in 85% yield, as faintly pink crystals. These were purified from water (pasty) or alcohol and ether; m.p. 200–210°, $(\alpha)_D^{20}$ +31.4° (alcohol, *c*, 0.4).

Anal. Calc'd for $C_{23}H_{24}BrNO_3{+}3H_2O$: C, 55.6; H, 6.09; OCH_3, 0.0; Br, 18.1; H_2O, 10.9.
Found: C, 56.1; H, 6.23; OCH_3, 0.0; Br, 18.5; loss at 110°, 12.7.

The base was precipitated with bicarbonate and extracted (sparingly soluble) into ether in the presence of sodium dithionite; it was purified from 50% alcohol, m.p. 130–136°, $(\alpha)_D^{28}$ +12.3° (alcohol, *c*, 0.3).

Anal. Calc'd for $C_{23}H_{23}NO_3 + 0.5H_2O$: C, 74.6; H, 6.53; H_2O, 2.4.
Found: C, 74.3; H, 6.40; loss at 110°, 1.9.

Methylation. A solution of norphenyldihydrothebaine in methanol-ether (1:2) was treated with excess diazomethane. The product was an oil, whose hydrobromide (from alcohol) had the m.p. 86.5–89° (gas evol. at 97°); $(\alpha)_D^{28}$ +21.4° (alcohol, *c*, 0.3).

Anal. Calc'd for $C_{26}H_{30}BrNO_3$: 3 OCH_3, 19.2. Found (dried sample): OCH_3, 20.9.

The *methiodide*, from methanol, had m.p. 195–197°, $(\alpha)_D^{28}$ +19.2° (alcohol, *c*, 0.34).

Anal. Calc'd for $C_{27}H_{32}INO_3$: 3 OCH_3, 17.0. Found: OCH_3, 16.4.

Attempted oximation. Norphenyldihydrothebaine, suspended in water, was heated with two equivalents of hydroxylamine hydrochloride at 100° for 75 min. The base went into solution and on cooling colorless needles of a hydrochloride separated. The base recovered from this melted at 132–137°, no depression in mixture with starting material.

Phenyldihydrothebaine methyl ether, obtained by the action of diazomethane on (+) α-phenyldihydrothebaine was a sirup, whose hydrobromide melted at 86–88° (gas evol. at 99°) and had $(\alpha)_D^{25}$ +21.9° (alcohol, *c*, 0.33).

Anal. Calc'd for $C_{26}H_{30}BrNO_3$: 3 OCH_3, 19.2. Found: OCH_3, 18.9.

The *methiodide* had the m.p. 196–197.5°, $(\alpha)_D^{28}$ +20.7° (alcohol, *c*, 0.34).

Anal. Calc'd for $C_{27}H_{32}INO_3$: 3 OCH_3, 17.0. Found: OCH_3, 16.7.

DEGRADATION OF THE METHYLDIHYDROTHEBAINONES

Methyldihydrothebainone methine. A suspension of 3.3 g. of methyldihydrothebainone methiodide (7) in 20 ml. of 30% KOH was boiled vigorously for 15 min. The resinous product was hydrolyzed with water and CO_2, and brought into ether, which yielded 1.5 g. of crystals (66%); from ethyl acetate, felted needles, m.p. 164–165° (darkens); $(\alpha)_D^{20}$ +163° (alcohol, *c*, 1.0); diazosulfanilic acid test intense red.

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.9; H, 8.25.
Found: C, 72.6; H, 8.22.

The *methiodide*, from methanol, had the m.p. 246–249° (evac. tube), $(\alpha)_D^{20}$ +117° (alcohol, *c*, 0.51).

Anal. Calc'd for $C_{21}H_{30}INO_3$: C, 53.5; H, 6.41.
Found: C, 53.2; H, 6.81.

Methyldehydrothebenone. The above methine methiodide was degraded by boiling for 5 min. with 30% KOH. The suspension of granular material was acidified with HCl, and the precipitate recrystallized from alcohol (88% yield), and sublimed at 150°/0.1 mm., m.p. 183–184°; $(\alpha)_D^{20}$ +262° (acetone, *c*, 0.52); diazosulfanilic acid test negative.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.0; H, 7.09.
Found: C, 75.7; H, 7.40.

Isomethyldihydrothebainone methine. Isomethyldihydrothebainone (7) was converted to the methiodide in boiling acetone, and the hygroscopic crystals immediately boiled for 15 min. with 30% KOH. The resin was treated with water and CO_2 and brought into benzene, which yielded 0.8 g. of pink crystals; purified from ethyl acetate and sublimed at 150°/0.1 mm., m.p. 193°, $(\alpha)^{20}_{D}$ +231° (alcohol, *c*, 0.2); diazosulfanilic acid test intense red.

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.9; H, 8.25.
Found: C, 72.5, 72.4; H, 8.90, 8.51.

Isomethyldehydrothebenone. The methine was converted to the amorphous methiodide, which was boiled 4 min. with 30% KOH. The resin was triturated with dil. HCl and ether; the ether gave a crystalline product in poor yield; from alcohol, m.p. 116.5–117°, $(\alpha)^{20}_{D}$ +252° (alcohol, *c*, 0.49); diazosulfanilic acid test negative.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.0; H, 7.09.
Found: C, 75.9; H, 7.09.

SUMMARY

Phenylmagnesium bromide reacts with thebaine to give two isomeric phenyldihydrothebaines, designated as (+) α and (+) δ. By heat treatment the (+) α isomer rearranges to a (−) δ form, and the (+) δ isomer to a (−) α form. The isomerism of the α and δ series is shown to be due to a difference in configuration at the asymmetric atom to which nitrogen is attached.

By hydrogenolysis, the nitrogen-containing ring of the (+) α and (+) δ isomers is opened, to give a single (+) phenyltetrahydrothebaimine; the (−) α and (−) δ isomers give similarly a (−) phenyltetrahydrothebaimine. These optical antipodes form a well-defined racemate.

The degradation of the phenyldihydrothebaines through isomethines to nitrogen-free products is described. The great stability of the ring system, the retention of the vinyl group in the final step of exhaustive methylation, and other peculiarities of the phenyldihydrothebaines are not explicable on the basis of the accepted thebaine formula. Since thebaine is related to morphine through dihydromorphine dimethyl ether, this also casts doubt on the structure of morphine.

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[Contribution from the Division of Physiology,
National Institute of Health]

BIGUANIDE AND THIOUREA DERIVATIVES OF QUINOLINE[1]

EVERETTE L. MAY and ERICH MOSETTIG

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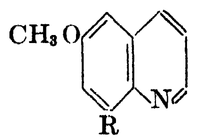
The outstanding value, as antimalarials, of Chloroquin[2] and Plasmochin[3] on the one hand and the exceedingly interesting properties, in experimental and clinical malaria, of Paludrine[4] on the other, prompted us to attempt the synthesis of drugs carrying a biguanidyl group in place of the side chain in Chloroquin and Plasmochin. In view of the low toxicity of Paludrine and of its analogs in the phenanthrene series (1, 2), one could reasonably expect a similar property in the planned compounds.

Many attempts, under varied conditions, to induce 4-amino-7-chloroquinoline to react with cyanoguanidine or isopropylcyanoguanidine failed. Moreover, we did not succeed in converting this aminoquinoline to the corresponding isothiocyanate, a potential intermediate to biguanide derivatives (1, 2). These failures may be attributed to the distinct character of the 4-amino group in the quinoline nucleus (3, 4, 5, 6).

In contrast to our experience with 4-amino-7-chloroquinoline, no difficulties were encountered in bringing about the addition of the cyanoguanidines to 8-amino-6-methoxyquinoline to give satisfactory yields of 1-(6-methoxy-8-quinolyl)biguanide (I) and 1-isopropyl-5-(6-methoxy-8-quinolyl)biguanide (II)[5]. Furthermore, 8-amino-6-methoxyquinoline and isopropylisothiocyanate produced readily, 1-isopropyl-3-(6-methoxy-8-quinolyl)thiourea (III) which was converted, with methyl iodide, to 1-isopropyl-3-(6-methoxy-8-quinolyl)-2-methyl-2-thiopseudourea (IV).



I R = $NHC(:NH)NHC(:NH)NH_2$
II R = $NHC(:NH)NHC(:NH)NH\text{-}i\text{-}C_3H_7$
III R = $NHC(:S)NH\text{-}i\text{-}C_3H_7$
IV R = $N:C(SCH_3)NH\text{-}i\text{-}C_3H_7$

None of the compounds tested showed any effectiveness against blood-inoculated *gallinaceum* malaria (7).

Acknowledgment. We wish to express our thanks to Dr. Reynold C. Fuson for supplying us with 4-amino-7-chloroquinoline. The microanalyses were carried out by C. A. Kinser and Betty Mount of this Institute.

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[1] Attempts to find New Antimalarials XXV.

[2] 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

[3] 6-Methoxy-8-(4-diethylamino-1-methylbutylamino)quinoline.

[4] 1-(p-Chlorophenyl)-5-isopropylbiguanide.

[5] While this paper was in press, we were informed by private communication that Curd, Hendry, Kenney, Murray, and Rose, of Imp. Chem. Ind., Ltd., have prepared, among others, compound II. Their work will be published in the Journal of the Chemical Society.

EXPERIMENTAL[6]

Experiments with 4-amino-7-chloroquinoline (V). A mixture of the hydrochloride of V and cyanoguanidine or 1-cyano-3-isopropylguanidine (1) in boiling alcohol gave V-HCl. When the alcoholic mixture was heated in a sealed tube at temperatures of 150–190° only 40% of the V-HCl was recovered, and intractable oily hydrochlorides were obtained. Fusion of the reactants gave essentially the same results. A mixture of the components in boiling, aqueous copper sulfate yielded only starting material.

When V was treated with carbon disulfide and aqueous (8) or alcoholic ammonia or alcoholic sodium hydroxide, it was recovered quantitatively. In the course of these reactions, the nitrate and acid sulfide salts were obtained. Efforts to prepare the diquinolylthiourea by refluxing V and carbon disulfide together in pyridine, alcohol, or dilute aqueous alcoholic potassium hydroxide were essentially without success.

4-Amino-7-chloroquinoline nitrate crystallized from alcohol-water in needles, m.p. 274° (dec.).

Anal. Calc'd for $C_9H_8ClN_3O_3$: C, 44.7; H, 3.3.
Found: C, 44.9; H, 3.5.

4-Amino-7-chloroquinoline acid sulfide crystallized from chloroform in small, yellow prisms, m.p. 150° (dec.).

Anal. Calc'd for $C_9H_9ClN_2S$: C, 50.8; H, 4.3.
Found: C, 50.8; H, 3.9.

1-(6-Methoxy-8-quinolyl)biguanide hydrochloride (NIH 2303)[7] *(I).* A mixture of 5 g. of 8-amino-6-methoxyquinoline hydrochloride, 2 g. of cyanoguanidine, and 25 ml. of 95% ethanol was refluxed for four hours to give 3.0 g. (43%) of I, m.p. 238–240°. It crystallized from 80% ethanol in needles, m.p. 243–245.5° (dec.).

Anal. Calc'd for $C_{12}H_{15}ClN_6O$: C, 48.9; H, 5.1.
Found: C, 49.3; H, 5.1.

The base, prepared from the hydrochloride with dilute, aqueous ammonia, crystallized from ethanol in oblong plates of m.p. 165.5–166.5° (gas evolution). The analysis indicated 0.5 mole of solvate water, but loss-in-weight determinations for the percentage of water gave no consistent results.

Anal. Calc'd for $C_{12}H_{14}N_6O + 0.5H_2O$: C, 53.9; H, 5.7.
Found: C, 54.3; H, 5.7.

1-Isopropyl-5-(6-methoxy-8-quinolyl)biguanide hydrochloride (NIH 2302) (II). A mixture of 3.5 g. of 8-amino-6-methoxyquinoline hydrochloride, the 1-cyano-3-isopropylguanidine from the desulfurization of 3 g. of 1-isopropyl-2-methyl-2-thiopseudourea (1), and 20 ml. of 95% ethanol gave, after refluxing for six hours, 2.5 g. (50%) of II hydrochloride, m.p. 230–233°; needles from 95% ethanol, m.p. 234–236°.

Anal. Calc'd for $C_{15}H_{21}ClN_6O$: C, 53.5; H, 6.3.
Found: C, 53.7; H, 6.4.

1-Isopropyl-3-(6-methoxy-8-quinolyl)thiourea (NIH 2309) (III). A mixture of 7.5 g. of 8-amino-6-methoxyquinoline, 4.4 g. of isopropylisothiocyanate (1, 9), and 30 ml. of ethanol was refluxed for two hours, diluted somewhat with water, and cooled in ice to give 7.1 g. (60%) of III, m.p. 135–137°. It crystallized from methanol in rods of m.p. 136–137.5°.

Anal. Calc'd for $C_{14}H_{17}N_3OS$: C, 61.1; H, 6.2.
Found: C, 61.0; H, 6.3.

1-Isopropyl-3-(6-methoxy-8-quinolyl)-2-methyl-2-thiopseudourea (NIH 2812) (IV). Six grams of III and 50 ml. of absolute ethanol were treated slowly with 1.5 ml. of methyl iodide. After refluxing gently for ten minutes, conc'd ammonia and water were added to give, after long standing and finally ice-cooling, 3.5 g. (55%) of IV, m.p. 71–77°. After two recrystallizations from aqueous methanol, it melted at 82–83.5°; prisms.

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[6] All melting points given are uncorrected.

[7] Compounds tested are designated by an NIH number; results on these were obtained too late to be classified in the Survey monograph.

Anal. Calc'd for $C_{15}H_{19}N_3OS$: C, 62.1; H, 6.6.

Found: C, 62.2; H, 6.6.

SUMMARY

Some biguanide and thiourea derivatives of 8-amino-6-methoxyquinoline were prepared for antimalarial tests.

Attempts to prepare biguanide derivatives from 4-amino-7-chloroquinoline failed.

BETHESDA 14, MARYLAND

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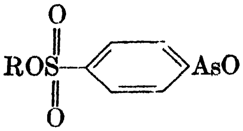
[Contribution No. 87 from the Research Laboratories of Hoffmann-La Roche, Inc.]

ARSENICALS. PART I. SULFONYLOXY, SULFONAMIDO, AND BENZYLOXY DERIVATIVES OF PHENYLARSONIC ACIDS AND THEIR REDUCTION PRODUCTS

H. HERBERT FOX

Received July 10, 1947

The experimental work in this paper was completed several years ago and was based, in the main, upon the idea of combining within the framework of one molecule, structures reminiscent of the sulfonamides and the aromatic arsenicals, in the hope of effecting a significant increase in spirochetocidal, trypanocidal, or bacteriostatic activity. An increasing number of arsenicals containing sulfonyl residues have appeared in the recent literature (1, 2, 3, 4, 5, 6). To date, however, most of the compounds reported have had the sulfur and arsenic atoms linked directly to the same nucleus, (formula I) whereas in the present study, the sulfur atom has been linked to the arsenic-bearing nucleus *via* an oxygen or nitrogen bridge (formula II and III).



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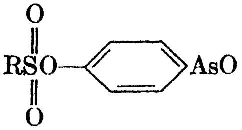
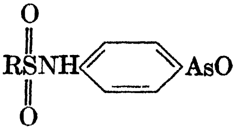


II



III

The synthesis of both types of compounds was effected by condensing *p*-acetamidobenzenesulfonyl chloride with the appropriate arsenical. In the case of arsanilic acid, the condensation did not take place and the arsanilic acid was recovered unchanged. Upon reduction of the arsono group to the arsenoxide, however, condensation was easily effected. With 3-amino-4-hydroxyphenylarsonic acid, condensation took place readily, but not in the anticipated direction. The *p*-acetamidobenzenesulfonyl chloride reacted only with the hydroxyl group and left the amino group untouched. The resistance of the amino group to the Hinsberg reaction may be attributed to the influence of the arsonic acid moiety.

In addition to the two types of compounds outlined above, another series was prepared with a view to ascertaining the influence of the benzyl group when used to block the hydroxyl group of 3-amino-4-hydroxyphenylarsonic acid and its reduction products. Two of the compounds in this series were previously reported by Balaban (7), who prepared 3-nitro-4-benzyloxyphenylarsonic acid in 36% yield by heating 3-nitro-4-hydroxyphenylarsonic acid with benzyl chloride for 20 hours in alkaline solution. In the present study, slight modification of conditions resulted in a 74.5% yield of the same compound in 2 hours.

In order to hydrolyze the acetamido group in the presence of hydrolysis-sensitive sulfonyloxy and sulfonamide linkages, recourse was had to the method of Kwartler (8) involving the use of alcoholic hydrogen chloride and a small quantity of concentrated hydrochloric acid at room temperature.

The trypanocidal and spirochetocidal activity of the arsenicals described in this report was tested by R. J. Schnitzer of the Chemotherapy Division of these laboratories. Tests were conducted in rabbit syphilis and on mice infected with *T. equiperdum* and *Borrelia novyi*. Though some of the compounds were quite active in rabbit syphilis and relapsing fever (*Borrelia novyi*), none of them could be considered superior to Mapharsen. Some miscellaneous tests conducted by Schnitzer also showed that none of the compounds possessed bactericidal activity *in vivo*.

Acknowledgment. The author wishes to acknowledge his gratitude and appreciation to Dr. H. M. Wuest for suggestions made at the time this work was in progress.

The author is also indebted to Dr. A. Steyermark for the microanalyses.

EXPERIMENTAL

All melting points are corrected.

4-(p-Acetamidobenzenesulfonamido)phenylarsenoxide dihydrate. Twenty grams of *p*-aminophenylarsenoxide (obtained by the reduction of arsanilic acid with phenylhydrazine) and 25 g. of *p*-acetamidobenzenesulfonyl chloride are dissolved in acetone and 8 g. of pyridine are added to the solution. Heat is evolved and the mixture separates into 2 phases, the acetone is removed *in vacuo*, and the residue is dissolved in dilute sodium hydroxide. The solution is chilled and the product is precipitated at *p*H 7 with acetic acid. The slightly gummy precipitate hardens on standing. Repeated precipitation from dilute ammonium hydroxide with dilute acetic acid results in a yield of 27 g. of white powder melting at 198°.

Anal. Calc'd for $C_{14}H_{13}AsN_2O_4 \cdot 2H_2O$: As, 18; Mol. wt., 416.

Found: As, 17.8; Mol. wt. (iodine titration), 420.

4-(p-Aminobenzenesulfonamido)phenylarsenoxide dihydrate. The chemotherapeutic properties of this compound were reported by Eagle, *et al.* (9) who obtained the material from the Squibb Institute. Since no preparative procedure was given in their report, the synthesis is described here.

Ten grams of the acetyl compound prepared above, in 100 cc. of 25% methyl alcoholic hydrogen chloride and 4 cc. of concentrated hydrochloric acid are permitted to stand at room temperature for 48 hours. The bulk of the alcohol is then removed under vacuum and the residue is dissolved in water and filtered. The filtrate on treatment with ammonium hydroxide to slight alkalinity yields 6.9 g. of the desired product. The compound is obtained as a white powder and has no definite melting point.

Anal. Calc'd for $C_{12}H_{11}AsN_2O_3S \cdot 2H_2O$: As, 20.1; Mol. wt., 374.

Found: As, 20.2, 20.1; Mol. wt. (iodine titration), 366.

3-Amino-4-(p-acetamidobenzenesulfonyloxy)phenylarsonic acid. To 25 g. of 4-hydroxy-3-aminophenylarsonic acid [prepared by the reduction of the corresponding nitro compound with Raney nickel and hydrogen according to the method of Stevinson & Hamilton (10)] dissolved in 199 cc. of 2 *N* sodium hydroxide is added 35 g. of *p*-acetamidobenzenesulfonyl chloride in acetone. The mixture is warmed on the steam-bath for several minutes, diluted with water, and acidified to *p*H 3 with hydrochloric acid. The product precipitates out and is recrystallized from dilute methyl alcohol; yield 42 g. of fine white needles, m.p. (decomp.) 250°. The product does not give a phenol test and does give a test for a free amine. It is therefore the hydroxyl group which has been blocked.

Anal. Calc'd for $C_{14}H_{15}AsN_2O_7S \cdot 2H_2O$: As, 16.1. Found: As, 16.0

3-Amino-4-(p-aminobenzenesulfonyloxy)phenylarsonic acid. Deacetylation of the corresponding acetyl compound according to the method of Kwartler (8) yielded a white crystalline product. Upon recrystallization from hot water, long white needles of indefinite melting point are obtained.

Anal. Calc'd for $C_{12}H_{13}AsN_2O_6S \cdot H_2O$: As, 18.5. Found: As, 18.5, 18.3.

3-Amino-4-(p-acetamidobenzenesulfonyloxy)phenylarsenoxide. Three grams of the corresponding arsonic acid dissolved in methyl alcohol is refluxed with 2.5 g. of phenylhydrazine for one hour. The methyl alcohol is then removed under vacuum and the residue is treated with an excess of 2 *N* sodium hydroxide. The alkaline mixture is extracted several times with ether and then is neutralized with acetic acid to yield the desired arsenoxide. Purification is effected by solution in dilute sodium hydroxide, treatment with Norit, and reprecipitation with dilute acetic acid; yield 1.3 g. of white powder, m.p. 171–176°.

Anal. Calc'd for $C_{14}H_{13}AsN_2O_5S \cdot H_2O$: As, 18.1; Mol. wt., 414.
Found: As, 18.2; Mol. wt. (iodine titration), 420.

3-Amino-4-(p-aminobenzenesulfonyloxy)phenylarsenoxide. In 100 cc. of 2 *N* hydrochloric acid containing 0.5 g. of potassium iodide is dissolved 6.1 g. of the corresponding arsonic acid and the resulting solution is treated with a stream of sulfur dioxide for 4 hours at room temperature. At the end of this time, the mixture is cooled and neutralized with ammonium hydroxide. The resulting white precipitate is filtered, washed with water, and dried; yield approximately 5 g. of product melting indefinitely, but below 150°.

Anal. Calc'd for $C_{12}H_{11}AsN_2O_4S \cdot 2H_2O$: As, 19.3; Mol. wt., 390.
Found: As, 19.1; Mol. wt. (iodine titration), 386.

4,4'-bis(p-Acetamidobenzenesulfonyloxy)-3,3'-diaminoarsenobenzene. A solution of 5 g. of the corresponding arsonic acid in 10 cc. of 2 *N* sodium hydroxide and 150 cc. of water is added to a solution of 50 g. of sodium hydrosulfite and 10 g. of magnesium chloride in 400 cc. of water. The mixture is warmed to 55–60° with stirring for 2 hours. The product precipitates out as a yellow powder which may be purified by solution in acetone and reprecipitation with benzene; m.p. 177–183°, yield 4.3 g.

Anal. Calc'd for $C_{28}H_{26}As_2N_4O_8S_2$: Acetyl, 11.3. Found: Acetyl, 10.9.

4,4'-bis(p-Aminobenzenesulfonyloxy)-3,3'-diaminoarsenobenzene. Three grams of the corresponding arsonic acid are reduced with sodium hydrosulfite as described above to yield 2.5 g. of pale yellow powder. The product is purified by repeated solution in acetone and reprecipitation with benzene and finally by solution in acetone and reprecipitation with water; m.p. 139.5°.

Anal. Calc'd for $C_{24}H_{22}As_2N_4O_6S_2 \cdot H_2O$: As, 21.6. Found: As, 21.6.

3-Nitro-4-benzyloxyphenylarsonic acid. A mixture of 25 g. (1 mole) of 3-nitro-4-hydroxyphenylarsonic acid, 36 g. (3 moles) of benzyl chloride, 48.5 cc. (3 moles) 6 *N* sodium hydroxide, and 200 cc. of water is refluxed for 2 hours. The reaction mixture is kept alkaline by the addition of sodium hydroxide if necessary. The mixture is then cooled, extracted twice with ether, and the aqueous phase is acidified with acetic acid. The resulting precipitate (26 g. or 74.5%) is recrystallized from water to yield fine white needles melting at 250°.

Anal. Calc'd for $C_{13}H_{12}AsNO_6$: As, 21.2. Found: As, 20.7.

3-Amino-4-benzyloxyphenylarsonic acid. Twenty grams of the nitro compound is dissolved in a mixture consisting of 74 cc. of 1 *N* sodium hydroxide, 180 cc. of water, and 550 cc. of methyl alcohol. The mixture is then reduced in the presence of Raney nickel with hydrogen at room temperature and 50 pounds pressure. Upon completion of reduction, the methyl alcohol is removed under vacuum and the aqueous residue is acidified with dilute acetic acid to yield a tan precipitate (17 g. or 78%). The product is recrystallized from dilute alcohol and is obtained in the form of slightly tan needles melting (with previous darkening) at 248–249°. Balaban reported blackening at *ca* 220°.

Anal. Calc'd for $C_{13}H_{14}AsNO_4$: As, 23.2. Found: As, 22.8.

3-Amino-4-benzyloxyphenylarsenoxide. Ten grams of the arsonic acid is suspended in 100 cc of 2 *N* hydrochloric acid containing 0.2 g. of potassium iodide. The mixture is stirred and sulfur dioxide is passed in at room temperatue until all of the arsonic acid has gone into solution (*ca* 8 hours). The mixture is kept in the refrigerator overnight and is then treated with ammonium hydroxide. The resulting precipitate is redissolved in dilute sodium hydroxide and reprecipitated with dilute acetic acid to yield 6.2 g. of a white powder; m.p. 67–68°.

Anal. Calc'd for $C_{13}H_{12}AsNO_2 \cdot H_2O$: As, 24.4; Mol. wt., 307.
Found: As, 24.4; Mol. wt. (iodine titration), 306.5.

4,4'-bis (Benzyloxy)-3,3'-diaminoarsenobenzene dihydrochloride. A solution of 5 g. of the arsonic acid is reduced with sodium hydrosulfite as described above to yield 4 g. of the arseno compound. The free base is dissolved in acetone and reprecipitated with dilute hydrochloric acid. The hydrochloride thus formed is dissolved in glacial acetic acid and reprecipitated with a large excess of very dilute hydrochloric acid. For final purification the product is dissolved in methyl alcohol and reprecipitated with ether. It is obtained as a yellow powder melting at 155–159°.

Anal. Calc'd for $C_{26}H_{24}As_2N_2O_2 \cdot 2HCl \cdot H_2O$: As, 23.6. Found: As, 23.6.

SUMMARY

This report concerns the preparation of 3-amino-4-(*p*-acetamidobenzenesulfonyloxy)phenylarsonic acid, 4-(*p*-acetamidobenzenesulfonamido)phenylarsenoxide, 3-nitro-4-benzyloxyphenylarsonic acid and the derivatives obtained from these compounds by reduction of the arsono groups and/or deacetylation.

None of the compounds possessed outstanding trypanocidal or spirochetocidal activity.

NUTLEY, N. J.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

REACTIONS OF 1,2,3,4-TETRAHYDROPHENANTHRENE AND DERIVATIVES. IV. ALKYL DERIVATIVES AND ANTIMALARIAL DRUGS[1, 2]

W. E. BACHMANN AND J. R. DICE[3]

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An investigation has been made of the acetylation, succinoylation, and sulfonation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. In continuation of the program on antimalarial drugs outlined previously (1, 2), some amino alcohol derivatives of 4-methyl-1,2,3,4-tetrahydrophenanthrene and some derivatives of 9-methyl-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-1,2,3,4-tetrahydrophenanthrene were prepared.

Acetylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene by means of a Perrier modification of the Friedel-Crafts reaction gave 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (I). In agreement with Bachmann and Cronyn (3) this method gives only the 9 isomer, uncontaminated by any of the 7 isomer. The position of the acetyl group was proved by Clemmensen reduction to 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene which was identical with the compound prepared by the following different method. 4-Ethyl-1-acetylnaphthalene (4) was allowed to react with methyl bromoacetate and zinc to yield the methyl ester of β-(4-ethyl-1-naphthyl)-β-hydroxybutyric acid. The hydroxy ester was converted to the chloro ester which was dehydrohalogenated and hydrolyzed with alcoholic potassium hydroxide. The resulting β-4-ethyl-1-naphthylcrotonic acid (II) was reduced to the butyric acid with 2% sodium amalgam. γ-4-Ethyl-1-naphthylvaleric acid (III) was formed by means of an Arndt-Eistert synthesis and was cyclized to 1-keto-4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IV) with thionyl chloride and stannic chloride. Clemmensen reduction gave 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene identical with the hydrocarbon prepared previously. Dehydrogenation of samples with palladium-charcoal yielded 4-methyl-9-ethylphenanthrene in both cases.

4-Methyl-1,2,3,4-tetrahydro-9-phenanthroic acid was formed by sodium hypochlorite oxidation of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. A Willgerodt reaction on the acetyl compound yielded the amide of 4-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid which was hydrolyzed to the free acid. 4-Methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene was obtained by bromination of the acetyl compound. Beckmann rearrangement of the oxime of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene gave 4-methyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene which was hydrolyzed to 4-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene.

[1] The work on antimalarials was done in cooperation with the Committee on Medical Research.

[2] From the Ph.D. dissertation of J. R. Dice, 1946.

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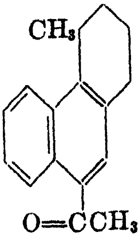
Sulfonation of 4-methyl-1,2,3,4-tetrahydrophenanthrene with chlorosulfonic acid gave 4-methyl-1,2,3,4-tetrahydrophenanthrene-9-sulfonic acid. By treating an aqueous solution of the potassium salt of the acid with aqueous bromine-sodium bromide solution (5), 4-methyl-9-bromo-1,2,3,4-tetrahydrophenanthrene was formed. The position of the groups was determined by adding the



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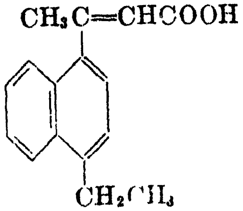

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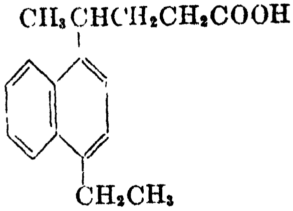

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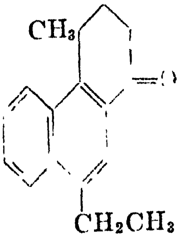

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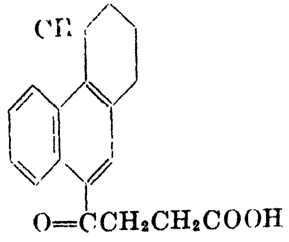

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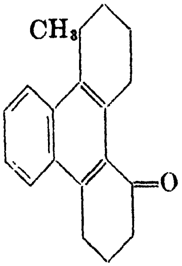

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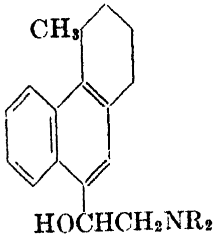

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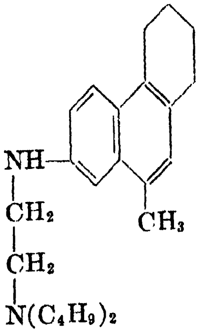

VIII

Grignard reagent prepared from the bromo compound to Dry Ice. The 4-methyl-1,2,3,4-tetrahydro-9-phenanthroic acid so obtained was identical with that prepared previously by oxidation. The homogeneity of the bromo derivative proved that sulfonation occurred only at the 9 position. Sulfonation in the 9 position is of interest since treatment of 1,2,3,4-tetrahydrophenanthrene with concentrated sulfuric acid yielded only the 7-sulfonic acid (6).

Succinoylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene formed β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid (V) which was subjected to a Clemmensen reaction to give γ-4-methyl-1,2,3,4-tetrahydro-9-phenanthrylbutyric acid. Cyclization of the acid chloride by stannic chloride resulted in the formation of 1-methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene (VI), which was reduced to 1-methyl-1-2,3,4,5,6,7,8-octahydrotriphenylene. 1-Methyltriphenylene [identical with the material prepared by Bachmann and Struve (7) by another method] was formed by dehydrogenation with palladium-charcoal. The position at which succinoylation occurred was proved by preparing β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid from 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene by a malonic ester synthesis.

Amino alcohol derivatives (VII) of 4-methyl-1,2,3,4-tetrahydrophenanthrene were prepared by coupling 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with a secondary amine and reducing the amino ketone with aluminum isopropoxide. 4-Methyl-9-β-di-*n*-butylamino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene, 4-methyl-9-β-N-piperidino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene, and 4-methyl-9-β-N-morpholino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene were prepared in this way.

Beckmann rearrangement of the oximes of 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (1) and hydrolysis of the resulting acetylamines gave 9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-9-amino-1,2,3,4-tetrahydrophenanthrene respectively. The 9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene was coupled with β-di-*n*-butylaminoethylbromide hydrobromide in the presence of sodium acetate and copper to yield 9-methyl-7-β-di-*n*-butylaminoethylamino-1,2,3,4-tetrahydrophenanthrene (VIII).

Complete pharmacological results are reported in the Survey of Antimalarial Drugs of the Committee on Medical Research.

Acknowledgment. We wish to thank the Abbott Laboratories for a fellowship to one of us (J. R. D.). We are grateful to Dr. R. C. Elderfield for generous gifts of amines and for information on the preparation of the amino alcohols by aluminum isopropoxide reduction.

EXPERIMENTAL[4]

4-Methyl-1,2,3,4-tetrahydrophenanthrene. 4-Methyl-1,2,3,4-tetrahydrophenanthrene (8, 9) was prepared by known methods: over-all yield from naphthalene, 60–65%. Evaporative distillation gave a colorless solid; m.p. 30–32° [reported as a colorless oil (9)]. The picrate melted at 116–117° [reported 117–119° (9)] and 4-methylphenanthrene prepared by dehydrogenation (9) melted at 52.0–52.5° [reported, 49° (8), 49–50° (9)].

Acetylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. 4-Methyl-1,2,3,4-tetrahydrophenanthrene was acetylated in 98% yield following the procedure given by Bachmann and Cronyn (3). Vacuum distillation at 0.02 mm. and 170–180° followed by several crystallizations from methanol-water yielded *4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene* as colorless, fluffy needles; m.p. 78.0–78.5°.

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[4] Micro-analyses by Micro-Tech Laboratories, Skokie, Illinois.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.
Found: C, 85.3; H, 7.7.

No 4-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene could be isolated from the reaction mixture.

Structure proof of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene; 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene. (a) *From 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene.* A mixture of 14 g. of amalgamated zinc, 18 ml. of hydrochloric acid, 18 ml. of glacial acetic acid, 2 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, and 15 ml. of toluene was refluxed for 24 hours with the addition of 5 ml. of hydrochloric acid every 6 hours. The toluene layer was washed with 10% hydrochloric acid, water, 10% sodium hydroxide, and water. Evaporative distillation of the solvent-free residue gave 1.6 g. (87%) of *4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene* as a colorless oil. The *trinitrobenzene derivative* formed yellow needles after three crystallizations from absolute alcohol; m.p. 97–98°.

Anal. Calc'd for $C_{23}H_{23}N_3O_6$: C, 63.2; H, 5.3; N, 9.6.
Found: C, 63.3; H, 5.2; N, 9.6.

Dehydrogenation of 240 mg. of 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene occurred readily upon heating to 200–210° in the presence of palladium-charcoal catalyst for 30 minutes (10) to give 210 mg. (88%) of *4-methyl-9-ethylphenanthrene* as a colorless oil. The *trinitrobenzene complex* formed yellow needles after several crystallizations from absolute alcohol; m.p. 143–144°.

Anal. Calc'd for $C_{23}H_{19}N_3O_6$: C, 63.7; H, 4.4; N, 9.7.
Found: C, 64.1; H, 4.2; N, 9.5.

(b) *From 1-ethylnaphthalene.* 1-Ethyl-4-acetylnaphthalene (1.98 g.), prepared by acetylation of 1-ethylnaphthalene according to Froschl and Horlass (4), was subjected to a Reformatsky reaction following the method of Bachmann, Cole, and Wilds (11), to give 2.73 g. of crude *methyl β-hydroxy-β-4-ethyl-1-naphthylpropionate* as a slightly yellow oil. The crude material was converted to the chloro ester and the latter was dehydrohalogenated and saponified (11) to *β-4-ethyl-1-naphthylcrotonic acid*, a colorless oil. *β-4-Ethyl-1-naphthylbutyric acid* was prepared from the above acid by reduction (11) with 2% sodium amalgam and was evaporatively distilled at 0.02 mm. and 160–180°; yield 1.75 g. of a colorless oil (73% over-all from 4-ethyl-1-acetylnaphthalene). By means of an Arndt-Eistert synthesis with oxalyl chloride (12), the side chain was extended by one carbon with the formation of *γ-4-ethyl-1-naphthylvaleric acid* in 60% yield. The *anilide* formed short colorless needles and melted at 109.5–110.5° after several recrystallizations from methanol.

Anal. Calc'd for $C_{23}H_{25}NO$: N, 4.8. Found: N, 4.5.

To a cooled solution of 0.95 g. of γ-4-ethyl-1-naphthylvaleric acid in 10 ml. of dry ether and 1 drop of pyridine was added 1.5 ml. of thionyl chloride. The mixture was allowed to stand at room temperature for 30 minutes and at 35° for 10 minutes, and the solvents were removed under reduced pressure. After two portions of dry benzene were added and then removed under reduced pressure, the *γ-4-ethyl-1-naphthylvaleryl chloride* was dissolved in 10 ml. of benzene and cooled to 0°, and a solution of 1.5 ml. of stannic chloride in 10 ml. of benzene was added rapidly. After standing at 0° for 30 minutes, the mixture was poured on ice, hydrochloric acid, and ether. The water layer was extracted with benzene, and the combined organic layers were washed with 10% hydrochloric acid, water, 10% sodium hydroxide, and water. *1-Keto-4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene* was a colorless oil after evaporative distillation at 0.01 mm. and 180–200°; yield 0.69 g. (76%). Its *oxime* after several recrystallizations from methanol-ethanol with Norit formed colorless needles; m.p. 174.5–175.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.8.

A mixture of 240 mg. of 1-keto-4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, 10 ml. of toluene, 1.7 g. of amalgamated zinc, 2.2 ml. of hydrochloric acid, and 2.2 ml. of glacial acetic acid was refluxed for 30 hours with the addition of 0.7-ml. portions of hydrochloric acid at approximately 6 hour intervals. The organic layer was washed with 10% hydrochloric acid, water, 10% sodium hydroxide, and water. Evaporative distillation yielded 210 mg. (93%) of 4-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene as a colorless oil. The trinitrobenzene derivative (m.p. 97–98°) melted at 97-98° when mixed with a sample prepared by method (a). The trinitrobenzene derivative of 4-methyl-9-ethylphenanthrene synthesized from the above material melted at 143–144° and showed no depression when mixed with the material from method (a).

Reactions of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. (a) *Haloform reaction.* A solution of 2 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene in 25 ml. of distilled dioxane was added to 50 ml. of sodium hypochlorite solution, prepared as described by Newman and Holmes (13), at 50–55°. After initial cooling the mixture was maintained at 60–70° with vigorous stirring for 2 hours. The cooled solution was poured on 100 ml. of hydrochloric acid, 2.0 g. sodium bisulfite, and ice. The *4-methyl-1,2,3,4-tetrahydro-9-phenanthroic acid* was collected and crystallized from acetone with Norit; m.p. 191–194°; yield, 1.9 g. (95%). After two recrystallizations from acetone and sublimation *in vacuo*, a sample melted at 202.0–202.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 80.0; H, 6.9.

(b) *Willgerodt reaction.* Using the method of Fieser and Kilmer (14) except that the time of heating was 24 hours and the temperature 175°, 1.1 g. (50%) of *4-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid amide* (m.p. 180.0-181.5°) was obtained from 2 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. After two recrystallizations from acetone and sublimation *in vacuo*, the amide was obtained as colorless needles; m.p. 186.0–186.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.5.

A mixture of 0.4 g. of the amide, 8.0 ml. of glacial acetic acid, 3.6 ml. of concentrated hydrochloric acid, and 0.8 ml. of water was refluxed for 24 hours. The hot solution was poured into 12 ml. of boiling hydrochloric acid. The colorless needles were treated with Norit in acetone, and sublimed *in vacuo;* m.p. 135–138°; yield, 0.32 g. (80%). A sample of *4-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid* crystallized several times from 90–100° petroleum ether and resublimed melted at 142.5–143.5°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.2; H, 7.3.

(c) *Bromination.* Bromination in the manner of Bachmann and Cronyn (3) gave 14.7 g. (74%) of *4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene* from 15.0 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. The product, a light yellow oil, was washed with 2% sodium bisulfite, 5% sodium bicarbonate, and water, and was used directly in subsequent reactions.

The *quaternary pyridine salt*, formed by adding a slight excess of pyridine and triturating with ether, was a colorless powder which was recrystallized five times from absolute alcohol with Norit; m.p. 230–231°.

Anal. Calc'd for $C_{22}H_{21}BrNO$: Br, 20.2. Found: Br, 19.5.

(d) *Oximation and rearrangement.* Following the procedure described by Bachmann and Cronyn (3), 10.0 g. of 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene was converted to the oxime. A sample of *4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* which had been recrystallized several times from methanol with Norit formed colorless needles; m.p. 137–138°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.0.

The crude oxime was subjected to a Beckmann rearrangement (3). A sample of *4-methyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene* crystallized from ethanol with Norit, sublimed *in vacuo*, and recrystallized three times from methanol, formed bright, colorless leaflets; m.p. 190–191°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.3.

The acetyl amine was hydrolyzed in the manner suggested (3), and the liquid amine was extracted with benzene. The *4-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene* weighed

6.0 g. (68% over-all yield from 4-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene) after removing the solvents, and darkened rapidly on exposure to air.

The *hydrochloride* was formed by passing dry hydrogen chloride into a benzene solution of the amine. The precipitate was recrystallized from methanol-ether, sublimed *in vacuo*, and recrystallized four times from methanol-ether as colorless needles; m.p. 259–261°.

Anal. Calc'd for $C_{15}H_{18}ClN$: N, 5.7. Found: N, 5.7.

The *picrate* crystallized from absolute alcohol in yellow needles; m.p. 203–205° dec.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: N, 12.7. Found: N, 12.3

Succinoylation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. A solution of 10 g. of 4-methyl-1,2,3,4-tetrahydrophenanthrene in 30 ml. of nitrobenzene was added slowly to a mixture of 18.6 g. of anhydrous aluminum chloride and 6.0 g. of succinic anhydride in 50 ml. of nitrobenzene cooled in an ice-salt bath. The mixture was stirred at −5° for 3 hours, placed in a refrigerator for 36 hours, and was poured on ice and hydrochloric acid. The nitrobenzene was removed with steam, the precipitated acid was dissolved in hot sodium bicarbonate solution, and the solution was filtered. Acidification with hydrochloric acid reprecipitated *β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid* as a gum which was dissolved in toluene, treated with Norit, and used in the next reaction.

γ-4-Methyl-1,2,3,4-tetrahydro-9-phenanthrylbutyric acid. A mixture of the above crude acid, 25 ml. of toluene, 65 g. of amalgamated zinc, 80 ml. of hydrochloric acid, and 80 ml. of glacial acetic acid was refluxed for 36 hours with the addition of three 26-ml. portions of hydrochloric acid at 6 hour intervals during the first part of the reaction. After the toluene layer had been washed with 10% hydrochloric acid and water, the solvents were flash-distilled and the residue was evaporatively distilled at 0.02 mm. The butyric acid formed an almost colorless glass on cooling but could not be crystallized; yield, 12.2 g. (85% from 4-methyl-1,2,3,4-tetrahydrophenanthrene).

1-Methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene. To a solution of 5.3 g. of the above acid in 50 ml. of dry benzene was added 4.1 g. of powdered phosphorous pentachloride in portions with vigorous stirring. After 1 hour at room temperature and 5 minutes at 85°, the solution was cooled in an ice-salt bath, and 10 g. of stannic chloride in 12 ml. of dry benzene was added in one portion. The mixture was stirred at 0° for 25 minutes and was poured on ice, 10% hydrochloric acid, and ether. The aqueous layer was extracted with ether and the combined organic layers were washed with 10% hydrochloric acid, 10% sodium hydroxide, and water. The alkaline wash removed most of the color and gave a slight precipitate on acidification. The solvents were removed from the organic layer by a current of air and the residue was evaporatively distilled at 0.01 mm.; 1-methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene solidified on standing; yield, 4.49 g. A sample recrystallized five times from methanol gave colorless prisms; m.p. 130–131°.

Anal. Calc'd for $C_{19}H_{20}O$: C, 86.3; H, 7.6.
Found: C, 85.5; H, 7.5.

The *oxime* crystallized from ethanol in tiny, colorless prisms; m.p. 173–175°.

Anal. Calc'd for $C_{19}H_{21}NO$: N, 5.0. Found: N, 5.2.

1-Methyl-1,2,3,4,5,6,7,8-octahydrotriphenylene. A mixture of 1.64 g. of the ketone, 15 ml. of toluene, 20 ml. of hydrochloric acid, 20 ml. of glacial acetic acid, and 16.5 g. of amalgamated zinc was refluxed for 24 hours with the addition of 6.5 ml. of hydrochloric acid every 6 hours. The toluene layer was washed as previously described, and the residue was evaporatively distilled at 0.01 mm. The colorless distillate (1.52 g.) crystallized slowly. In some cases it was necessary to purify the product *via* the picrate in order to obtain a satisfactory solid. Several crystallizations from acetone-absolute alcohol yielded 1-methyl-1,2,3,4,5,6,7,8-octahydrotriphenylene as colorless prisms; m.p. 91–92°.

Anal. Calc'd for $C_{19}H_{22}$: C, 91.1; H, 8.9.
Found: C, 90.4; H, 8.8.

The *picrate* crystallized from absolute alcohol as orange needles; m.p. 164–165°.

Anal. Calc'd for $C_{25}H_{25}N_3O_7$: N, 8.8. Found: N, 8.4.

A sample of 105 mg. of the octahydro compound was dehydrogenated to 1-methyltriphenylene by the method of Bachmann and Struve (7); yield, 70 mg. (70%); m.p. 87–89°. Three recrystallizations from alcohol-acetone gave colorless needles; m.p. 93–94°. A mixture with an authentic sample (7) melted at 93–94°. The picrate melted at 176–178° alone and when mixed with an authentic sample (7).

β-4-Methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid. Diethyl malonate (5.1 g.) was added to the sodium ethoxide prepared from 0.54 g. of sodium, 5 ml. of absolute alcohol, and 5 ml. of benzene, and the mixture was refluxed until homogeneous. Excess solvents were removed under reduced pressure until a small amount of solid formed, and 5 g. of 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene in 40 ml. of dry benzene was added with vigorous stirring. The mixture was allowed to stand for 24 hours and then refluxed for 2 hours. The solvents were removed in a current of air, and the residue was refluxed with 40 ml. of 45% potassium hydroxide and 25 ml. of alcohol for 1 hour. The solution was diluted with water and washed with ether-benzene. Acidification of the alkaline layer precipitated an oil which was extracted with two portions of ether. The ether was removed with a current of air, and the residue was heated at 170–180° for 15 minutes, with the evolution of carbon dioxide. The crude β-4-methyl-1,2,3,4-tetrahydro-9-phenanthroylpropionic acid was reduced by a Clemmensen reaction and cyclized to 1-methyl-5-keto-1,2,3,4,5,6,7,8-octahydrotriphenylene by the methods previously described; over-all yield from 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene, 1.0 g. (24%); m.p. 130–131° alone and when mixed with the ketone prepared by the first method.

Sulfonation of 4-methyl-1,2,3,4-tetrahydrophenanthrene. To a stirred, ice-cold solution of 10 g. of 4-methyl-1,2,3,4-tetrahydrophenanthrene in 25 ml. of dry carbon tetrachloride was added dropwise 6.42 g. of technical chlorosulfonic acid over a period of 30 minutes. The chlorosulfonic acid was covered with a layer of carbon tetrachloride to protect it from atmospheric moisture. After an additional 30 minutes of stirring at 0°, the solution was allowed to warm to room temperature, and 25 ml. of water was added. The carbon tetrachloride layer was washed with water, and the combined aqueous layers were neutralized with 25% potassium hydroxide until just basic to litmus. On cooling, 12.8 g. of the potassium salt of *4-methyl-1,2,3,4-tetrahydrophenanthrene-9-sulfonic acid* crystallized as colorless needles. A second crop raised the yield to 14.9 g.

To a vigorously stirred solution of 5.0 g. of the above potassium salt in 100 ml. of water at 70° was added rapidly a solution of 2.91 g. of bromine and 4.3 g. of sodium bromide in 15 ml. of water at 55° (5). Excess sodium bisulfite was added after 30 seconds, and the precipitated oil was extracted with two portions of carbon tetrachloride. Removal of the solvent by a current of air yielded 2.7 g. (62%) of *4-methyl-9-bromo-1,2,3,4-tetrahydrophenanthrene* as a colorless oil which crystallized slowly on standing; m.p. 58–60°.

The product was evaporatively distilled at 0.05 mm. and 100–120°, dissolved in benzene and passed through a 4-cm. column of alumina. After removal of the solvent in a current of air, two recrystallizations from absolute alcohol-acetone gave colorless prisms; m.p. 61–62°.

Anal. Calc'd for $C_{15}H_{15}Br$: C, 65.5; H, 5.5.
Found: C, 66.0; H, 5.7.

4-Methyl-1,2,3,4-tetrahydro-9-phenanthroic acid. A mixture of 0.5 g. of 4-methyl-9-bromo-1,2,3,4-tetrahydrophenanthrene, 0.05 g. of magnesium, 10 ml. of anhydrous ether, and a small crystal of iodine was refluxed for 5 hours. A small amount of ethylmagnesium bromide was added to start the reaction. The Grignard reagent was diluted with 50 ml. of ether and added dropwise to Dry Ice. After standing 16–24 hours the mixture was poured on ice and 10% hydrochloric acid. The aqueous layer was extracted with ether, and the combined organic layers were treated with three portions of 10% sodium hydroxide. Acidification of the basic extracts gave 0.31 g. of 4-methyl-1,2,3,4-tetrahydro-9-phenanthroic acid; m.p. 195–198°. Several recrystallizations from acetone with Norit gave colorless needles; m.p. 201.5–202.5°. When mixed with a sample of the tetrahydrophenanthroic acid obtained previously it melted at 201.5–202.5°.

Synthesis of antimalarial derivatives of 4-methyl-1,2,3,4-tetrahydrophenanthrene. (a)

4-Methyl-9-β-di-n-butylamino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene (SN. 12740). The method outlined in the preceding paper in this series (3) was used in the following condensations. The condensation of 4.9 g. of 4-methyl-9-bromoacetyl-1,2,3,4-tetrahydrophenanthrene with 4.0 g. of di-*n*-butylamine yielded the amino ketone, which was reduced directly to the amino alcohol with aluminum isopropoxide. Slow addition of dilute ethereal hydrochloric acid to the ether solution of the amino alcohol yielded the *hydrochloride* which formed tiny, colorless needles after four recrystallizations from acetone-ether; m.p. 197–198°.

Anal. Calc'd for $C_{25}H_{38}ClNO$: C, 74.3; H, 9.5; N, 3.5.
Found: C, 74.3; H, 9.8; N, 3.9.

(b) *4-Methyl-9-β-N-piperidino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene* (SN. 12129). The condensation of 4.9 g. of the bromo ketone and 2.7 g. of piperdine and reduction of the amino ketone were carried out as above. The *picrate* of the amino alcohol was prepared in absolute alcohol by adding 3.5 g. of picric acid. The solvent was removed in a current of air and the residue was triturated with ether in the cold. The crude picrate, recrystallized twice from absolute alcohol-acetone and triturated with ether, gave yellow needles; m.p. 160–162° dec.

Anal. Calc'd for $C_{28}H_{32}N_4O_8$: C, 60.9; H, 5.9; N, 10.1.
Found: C, 60.6; H, 5.9; N, 9.9.

(c) *4-Methyl-9-β-N-morpholino-α-hydroxyethyl-1,2,3,4-tetrahydrophenanthrene* (SN. 12130). The condensation of 4.9 g. of the bromo compound and 2.7 g. of morpholine, and reduction of the amino ketone were carried out as above. The yellow *picrate* melted at 180–182° dec.

Anal. Calc'd for $C_{27}H_{31}N_4O_9$: C, 58.4; H. 5.6; N. 10.1.
Found: C, 58.2; H, 5.6; N, 9.7.

Derivatives of 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene. The oxime of 30 g. of 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene (1) was prepared by the method of Bachmann and Cronyn (3). A sample of *9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* which was recrystallized four times from ethanol formed colorless leaflets; m.p. 174-175°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.0.

The oxime when subjected to a Beckmann rearrangement (3) gave *9-methyl-7-acetylamino-1,2,3,4-tetrahydrophenanthrene* as colorless leaflets after several recrystallizations from absolute alcohol; m.p. 233.5-234.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5. 6.

Hydrolysis of the acetylamine (3) formed a solid amine; crude yield, 15.6 g. (59% over-all from the acetyl compound); m.p. 88-91°. A sample of *9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene* recrystallized five times from ethanol gave colorless needles; m.p. 98.5–99.5°.

Anal. Calc'd for $C_{15}H_{17}N$: C, 85.3; H, 8.1; N, 6.6.
Found: C, 85.6; H, 8.2; N, 6.2.

The yellow *picrate* crystallized from absolute alcohol-ethyl acetate; m.p. 200–202° dec.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: N, 12.7. Found: N, 12.6.

The *hydrochloride* prepared by passing hydrogen chloride into a benzene solution of the amine melted at 258–260° dec. after two recrystallizations from absolute alcohol with Norit and sublimation at 0.01 mm.

Anal. Calc'd for $C_{15}H_{18}ClN$: Cl, 14.3. Found: Cl, 14.3.

9-Methyl-7-β-di-n-butylaminoethylamino-1,2,3,4-tetrahydrophenanthrene (SN. 12131). Using the method of Barnum and Hamilton (15), 5.0. g. of 9-methyl-7-amino-1,2,3,4-tetrahydrophenanthrene was coupled with 13.1 g. of β-di-*n*-butylaminoethylbromide hydrobromide, and the product was distilled several times at 0.02 mm. and 210–220°; yield of yellow oil, 2.7 g. The *oxalic acid salt* formed fine, colorless needles after several recrystallizations from absolute alcohol; m.p. 125–127°.

Anal. Calc'd for $C_{27}H_{40}N_2O_4$: C, 71.0; H, 8.8; N, 6. 1.
Found: C, 70.6; H, 8.7; N, 5.8.

Derivatives of 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. The oximation of 14.0 g. of 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (3) was carried out as above. A sample of *7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* crystallized several times from methanol as fine, colorless needles; m.p. 143–144°.

Anal. Calc'd for $C_{18}H_{21}NO$: N, 5.2. Found: N, 5.2.

The crude oxime was subjected to a Beckmann rearrangement (3) to give *7-ethyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene* which was crystallized several times from ethanol as colorless needles; m.p. 219–220°.

Anal. Calc'd for $C_{18}H_{21}NO$: N, 5.2. Found: N, 5.0.

Only 2.6 g. of the *7-ethyl-9-amino-1,2,3,4-tetrahydrophenanthrene* could be isolated after hydrolysis (3). It was an unstable solid which decomposed during all attempts to purify it.

The *picrate* crystallized from absolute alcohol as greenish-yellow needles; m.p. 184–185° dec.

Anal. Calc'd for $C_{22}H_{22}N_4O_7$: N, 12.3. Found: N, 12.5.

The *hydrochloride* was prepated by dissolving the amine in an excess of boiling 2% hydrochloric acid. The hot solution was filtered through Norit and was cooled for 12 hours. The long, colorless needles were crystallized from absolute alcohol and sublimed at 110–120° and 0.01 mm. as a colorless powder; m.p. 230–232° dec.

Anal. Calc'd for $C_{16}H_{20}ClN$: Cl, 13.6. Found: Cl, 14.1.

SUMMARY

1. Several new derivatives of 4-methyl-1,2,3,4-tetrahydrophenanthrene were prepared.

2. 1-Methyltriphenylene was synthesized by a new method.

3. New compounds derived from 9-methyl-7-acetyl-1,2,3,4-tetrahydrophenanthrene and 7-ethyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene are described.

4. Some compounds with antimalarial properties were prepared from the parent compounds.

ANN ARBOR, MICH.

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PIPERIDINE DERIVATIVES. PART II. 2-PHENYL- AND 2-PHENYLALKYL-PIPERIDINES[1]

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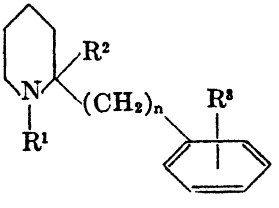
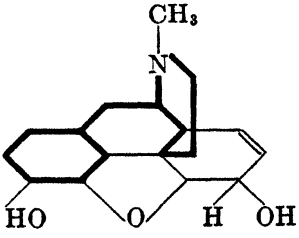
1-Methyl-2-benzylpiperidine (I, $R^1 = CH_3$, R^2, $R^3 = H$, $n = 0$) can be considered as an integral part of the structure of the morphine skeleton II, as indibycated the thickened lines.



I



II

It might be thefefore considered that a suitable substitution of this compound as in I ($R^1 = CH_3$, $R^2 = H$, $R^3 = OH$, $n = 0$) would give substances which, due to their spatial similarity to morphine and on account of a possible similarity of physico-chemical characteristics due to the presence of the basic nitrogen and phenolic hydroxyl group, might be expected to have morphine-like analgesic activity.

Compounds of the structure I as shown in Tables II and III have been prepared.

The method of synthesis of the structure of the compounds I where $n = 0$ is shown in the reaction scheme of Figure 1. Aryl- or aralkyl-magnesium halides were reacted with 1-methyl-2-piperidone. When the Grignard complex was decomposed in the normal manner, dehydration resulted, with formation of the 2-substituted-1,4,5,6-tetrahydro-1-methylpyridines. Similar experience is reported in the literature in the reaction of alkylmagnesium halides with the same piperidone (1). The tetrahydropyridines are unstable in air, oxidizing rapidly. Hydrogenation of the 1-methyl-4-phenyl-1,4,5,6-tetrahydropyridines at atmospheric or elevated pressure occurs with ease using Raney nickel or noble metal catalysts. When an alkoxyl substituent was present in the phenyl ring, dealkylation to the corresponding phenol and acylation of the hydroxyl group so formed proceeds normally. In order to obtain the 1-methyl-2-phenyl-2-piperidinol esters V, the Grignard complex was directly acylated with an acyl chloride or anhydride.

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The reaction scheme can also be carried out using benzylmagnesium halide to obtain compounds of the type I (n = 1). When, however, a substituent is desired in the benzyl nucleus this method is not satisfactory on account of the tendency of substituted benzyl magnesium halides to form α,β-diphenylethane derivatives in the Grignard reaction. A *p*-hydroxyl group was introduced into the phenyl ring of 2-benzylpiperidine by nitration, reduction and diazotization of the *p*-amino group.

In attempting to react 1-methyl-2-piperidone with cyclohexylmagnesium chloride, the desired product was not obtained, and the reaction mixture on working up yielding no identifiable material. However, when the Grignard complex was directly acylated with propionic anhydride, a monopropionyl product was obtained which apparently has the structure VII, and was isolated in the form of its dihydrochloride.

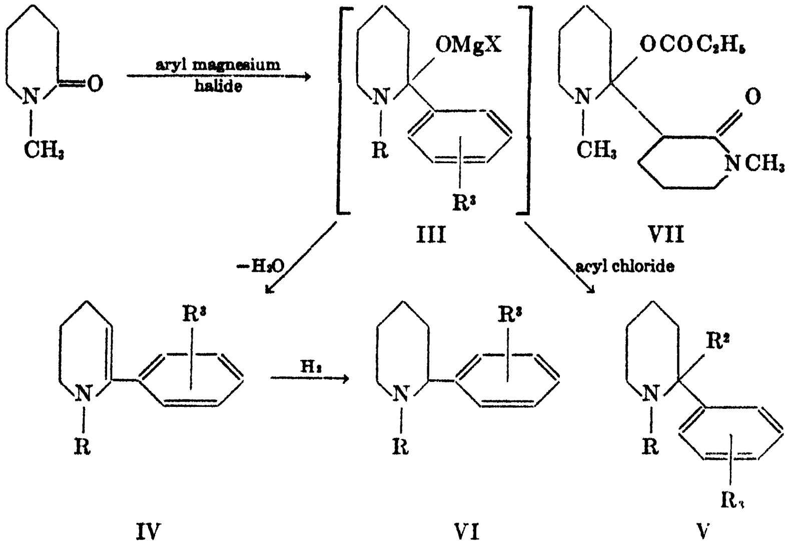

FIG. 1

R = alkyl
R² = acyloxy
R³ = hydrogen, alkoxy

Since the phenyl group of N-benzylpiperidines could be considered to occupy relatively the same position as the phenyl ring in 2-phenylpiperidine, 1-*p*-methoxyphenylpiperidine and 1-*p*-dimethylcarbamoxyphenylpiperidine were made in order to determine whether the analgesic activity displayed in the 2-phenyl series was retained.

The physical characteristics and the analyses of the compounds prepared are given in Tables I to IV.

TABLE I

1-Methyl 2-Substituted 1,4,5,6-Tetrahydropyridines (IV)

SUBSTANCE: 1,4,5,6-TETRAHYDROPYRIDINE	B.P.°,C (UNCORR)	FORMULA	M.W.	ANALYSIS					
				Calculated			Found		
				C	H	N	C	H	N
1-Methyl-2-*o*-methoxyphenyl-	oil 118–124/3 mm.	$C_{13}H_{17}NO$	203.2	76.8	8.4		75.7	8.2	
1-Methyl-2-*m*-methoxyphenyl-	oil 142/6 mm.	$C_{13}H_{17}NO$	203.2	76.8	8.4		76.2	7.8	
1-Methyl-2-*p*-methoxyphenyl-	oil 125/3 mm.	$C_{13}H_{17}NO$	203.2	76.8	8.4		*		
1-Methyl-2-*p*-methoxyphenyl- HCl	170 (m.p.)	$C_{13}H_{18}ClNO$	239.7			5.80			5.52
1-Methyl-2-[6′-methoxynaphthyl-(2′)]-	oil 175/2 mm.	$C_{13}H_{19}NO$	262.3	80.63	7.50	5.53	80.00	7.37	5.50
1-Methyl-2-benzyl-	120/2 mm.	$C_{13}H_{17}N$	187.2	83.4	9.1		82.1	8.95	

* The material was unstable and used directly for further syntheses.

TABLE II

1-METHYL 2-SUBSTITUTED PIPERIDINES

SUBSTANCE: PIPERIDINE		M P °,C (UNCORR)	FORMULA	M.W.	ANALYSIS					
					Calculated			Found		
					C	H	N	C	H	N
1-Methyl-2-*o*-methoxyphenyl-	HCl	147	$C_{13}H_{20}ClNO$	241.7			5.79			5.19
1-Methyl-2-*o*-hydroxyphenyl-	HCl	—	$C_{12}H_{18}ClNO$	227.7	63.1	7.91	6.15			
1-Methyl-2-*m*-methoxyphenyl-	HCl	—	$C_{13}H_{20}ClNO$	241.7	63.7	8.28	5.79	64.56	8.37	
1-Methyl-2-*m*-hydroxyphenyl-	HBr	~60	$C_{12}H_{18}BrNO$ $\frac{1}{2}$ H_2O	281.1	51.2	6.76		52.9	6.76	
1-Methyl-2-*p*-methoxyphenyl-	HCl	170 ether-acetone	$C_{13}H_{19}ClNO$	240.8	64.0	8.28	5.79			5.52
1-Methyl-2-*p*-hydroxyphenyl-	HBr	231 ether-acetone	$C_{12}H_{18}BrNO$	272.2	53.2	6.64		52.9	6.62	
1-Methyl-2-*p*-acetoxyphenyl-	HCl	189 ether-acetone	$C_{14}H_{20}ClNO_2$	269.7			5.18			5.03
1-Methyl-2-*p*-dimethylcarbamoxyphenyl-	HCl	145 ether-acetone	$C_{15}H_{23}ClN_2O_2$	298.7			9.38			9.18
1-Methyl-2-*p*-phenylmethylcarbamoxyphenyl-	HCl	140 ether-acetone	$C_{15}H_{25}ClN_2O_2$	360.7			7.76			7.56
1-Methyl-2-*p*-diethylcarbamoxyphenyl-	HCl	—	$C_{17}H_{27}ClN_2O_2$	330.7			8.47			8.50
1-Methyl-2-benzyl-	HCl	158–160	$C_{13}H_{20}ClN$	225.7	69.2	8.8		68.0	8.7	

1-Methyl-2-*p*-hydroxybenzyl-		153 benzene	$C_{13}H_{19}NO$	205.2	76.09	9.26	6.83	76.23	9.42	7.03
1-Methyl-2-*p*-dimethylcarbamoxybenzyl-	HCl	166 EtOAc	$C_{16}H_{25}ClN_2O_2$	312.7			8.96			9.02
1-Methyl-2-[6′-methoxynaphthyl-(2′)]-	HCl	235 acetone-methanol	$C_{17}H_{22}ClNO$	291.7	70.00	7.54	4.87	69.97	7.67	4.80
1-Methyl-2-[6′-hydroxynaphthyl-(2′)]-	HCl	235 acetone-MeOH	$C_{16}H_{20}ClNO$	277.7	69.7	7.21		69.11	6.89	
1-Methyl-2-[6′-dimethylcarbamoxy-naphthyl-(2′)]-	HCl	220 acetone	$C_{19}H_{25}ClN_2O_6$	384.7	65.40	7.22	8.02	65.36	7.33	7.88

TABLE III

2-PIPERIDINOL ESTERS (I, R_2 = ACYLOXY)

SUBSTANCE: PIPERIDINE	DESCRIPTION	M.P., °C.	FORMULA	M W.	ANALYSIS					
					Calculated			Found		
					C	H	N	C	H	N
1-Methyl-2-benzyl-2-propionoxy- HCl	syrup*	—	$C_{16}H_{24}ClNO_2$	251.8	65.3**	7.77**		64.98	8.0	
1-Methyl-2-phenyl-2-acetoxy- HCl	syrup	—	$C_{14}H_{20}ClNO_2$	269.5	62.3	7.32	5.19	61.95	7.67	5.66
1-Methyl-2-phenyl-2-propionoxy- HCl	colorless prisms	119–120 (corr) acetone	$C_{15}H_{22}ClNO_2$	283.5	63.50	7.76	4.94	63.11	7.40	5.56
1-Methyl-2-(1′-methyl-2′-oxo-3′-piperidyl)-2-propionoxy di- HCl	hygroscopic colorless crystals	80	$C_{15}H_{26}N_2O_3$ 2 HCl·H_2O	373.3	48.28	8.04	7.51	48.10	7.86	7.32

* A mixture with dehydration product.

** Calculated for 90% ester and 10% 1-methyl-2-benzyl-1,4,5,6-tetrahydropyridine HCl.

Pharmacological results. The detailed pharmacological results will be reported elsewhere. The following general observations were made.

When a phenyl group is attached directly to the piperidine nucleus in the 2 position (compounds I, $R^1 = CH_3$, $R^2 = H$, $R^3 = H$, $n = 0$), the compound was inactive. A low analgesic activity was noted with substitution of the methoxyl groups in the phenyl nucleus. Little or no activity was found with free hydroxyl groups (I, $R^1 = CH_3$, $R^2 = H$, $R^3 = OH$, $n = 0$), and the acetylation of the hydroxyl groups also gave materials of only slight activity. However, on acylating the phenolic hydroxyl with a group more resistant to hydrolysis, as for example the dimethylcarbamyl group, increased activity was obtained the best compounds being those with *p*-substituents. The activity was not sufficient to be of practical interest. Replacing the phenyl with a β-naphthyl group reduced the activity. When the phenyl group was linked to the piperidine nucleus by a CH_2 group (I, $R^1 = CH_3$, $R^2 = H$, $R^3 = H$, $n = 1$), thus conforming more closely to the type I structure, it was found that the compound was inactive, and substitution in the ring of hydroxyl, methoxyl, or acyloxyl groups in the *p*-position did not change this. It would appear from this that strict adherence in this series to the relationship of the individual atoms in the morphine skeleton does not give the highest analgesic activity; in fact, here the compounds more closely related to morphine are less active than those more remote in structure.

1-Methyl-2-substituted piperidinol esters (I, R^2 = acyloxy, $R^3 = H$, $n = 0$ or 1) were without significant activity.

Increasing the length of the side chain to 2 carbon atoms yielding 2-phenethyl derivatives (I, R = alkyl, $R^2 = H$, R^3 = alkoxy, $n = 2$) gives compounds with low analgesic activity. These compounds were described in the previous paper of this series (2). The 1-*p*-acyloxybenzyl piperidines were inactive.

Acknowledgment. Most of the analyses of the compounds described in this paper were performed in the Microanalytical Division of these laboratories under the direction of Dr. A. Steyermark. The pharmacological results are due to Drs. N. Ercoli, R. H. K. Foster, and G. Lehman. We wish to express our thanks to these workers for their co-operation.

EXPERIMENTAL

1-Methyl-2-(p-methoxyphenyl)-1,4,5,6-tetrahydropyridine. Two-tenths mole of magnesium and 50 cc. of dry ether were placed in a three-necked flask provided with a ground sealed stirrer, dropping-funnel, and reflux condenser. To this was added 0.2 mole of *p*-bromoanisole in 50 cc. of ether. After the complete addition of the *p*-bromoanisole the ether solution was refluxed for one hour to complete the reaction. The flask was then cooled in an ice-bath and 0.2 mole of 1-methyl-2-piperidone in 100 cc. of ether was added. After the complete addition the mixture was refluxed with stirring for eight hours, during which the gummy complex became solid. This was decomposed with dilute hydrochloric acid, the ether layer separated, the aqueous layer saturated with sodium carbonate, extracted with ether and the ether solutions combined. The ether solution was dried, and the ether removed by distillation. On fractionation in vacuum, 1-methyl-2-(*p*-methoxyphenyl)-1,4,5,6-tetrahydropyridine was obtained having the b.p. 125° at 3 mm. By passing dry hydrochloric acid gas into a dry ether solution of the base, the hydrochloride, m.p. 175°, was obtained.

1-Methyl-2-(p-methoxyphenyl)piperidine hydrochloride. Twenty grams of 1-methyl-2-(*p*-methoxyphenyl)-1,4,5,6-tetrahydropyridine was dissolved in 100 cc. of absolute alcohol, 5 g. of Raney nickel added, and the reduction carried out under pressure of 50 pounds at room temperature. The pressure and the temperature are not critical and may vary up to 4000 pounds and 100°. The quantitative amount of hydrogen was adsorbed rapidly and when complete, the catalyst was filtered off and the alcohol removed from the filtrate. The crude 1-methyl-2-(*p*-methoxyphenyl)piperidine was dissolved in ether and dry hydrochloric acid gas passed in. The hydrochloride separated out as white crystals, m.p. 170°.

1-Methyl-2-(p-hydroxyphenyl)piperidine hydrobromide. Twenty grams of 1-methyl-2-(*p*-methoxyphenyl)piperidine base was dissolved in 50 cc. of acetic acid and 60 cc. of 30% hydrobromic acid in acetic acid was added. The solution was refluxed for four hours and then distilled in a vacuum to remove the acetic acid and excess hydrobromic acid. The residue was crystallized from alcohol, m.p. 231°.

1-Methyl-2-(p-dimethylcarbamoxyphenyl)piperidine hydrochloride. Twenty grams of 1-methyl-2-(*p*-hydroxyphenyl)piperidine hydrobromide was dissolved in 100 cc. of water and the solution saturated with potassium carbonate. The separated piperidine base was extracted with ether, the ether solution dried, and the ether removed by distillation. The free phenolic base was dissolved in 50 cc. of dry pyridine and 9 g. of dimethylcarbamyl chloride added. The solution was heated on a water-bath for three hours, when a further 9 g. of dimethylcarbamyl chloride was added and the solution heated for another hour. The solvent was removed in a vacuum, the residue dissolved in water, and the solution made alkaline with sodium hydroxide. The dimethylcarbamyl ester was extracted with ether, and after drying over potassium carbonate the solution was filtered and hydrogen chloride passed in. The product, 1-methyl-2-(*p*-dimethylcarbamoxyphenyl)piperidine hydrochloride melted at 145°.

1-Methyl-2-acetoxy-2-phenylpiperidine hydrochloride. The Grignard reagent prepared from 23.5 g. of freshly distilled bromobenzene (0.15 mole) and 3.6 g. of magnesium (0.15 mole) was reacted with 11.3 g. of 1 methyl-2-piperidone (0.1 mole) in the usual manner. The gum that formed soon hardened after addition of dry benzene. After refluxing for one hour the reaction was cooled and 20.4 g. (0.2 mole) of acetic anhydride in dry benzene added. The reaction was refluxed for several minutes, then left to stand overnight. It was decomposed with ice cold 6 *N* HCl and the product isolated in the usual manner.

Four grams of a thick oil, boiling at 185–198° at 5 mm. was obtained. This was converted to the hydrochloride, which was also a thick syrup (hygroscopic) and which could not be crystallized. It was submitted for analysis as such.

In a like manner 2-phenyl-2-propionoxy-1-methylpiperidine hydrochloride was prepared. This product was a white solid which crystallized from acetone in small prisms. Recrystallized twice, it melted at 119–120°.

1-Methyl-2-[6′-methoxynaphthyl-(2′)]-1,4,5,6-tetrahydropyridine. Eight grams of magnesium in a Grignard reaction apparatus was covered with 150 cc. of dry ether, a crystal of iodine was added, and a solution of 50 g. of 2-bromo-6-methoxynaphthalene in 150 cc. of dry benzene was added. It was refluxed on a water-bath; two cc. of ethyl bromide was added every hour until a total of 10 cc. had been added. At this time most of the magnesium had disappeared and the flask was cooled in an ice-bath, and a solution of 37 g. of 1-methyl-2-piperidone in 100 cc. of ether was added dropwise. The mixture was then refluxed for three hours and after cooling, it was decomposed with dilute hydrochloric acid. The hydrochloride of the tetrahydropyridine base separated out and was filtered off. This was converted to the free base by suspension in warm sodium hydroxide solution, extracted with ether, dried, and fractionated, b.p. 175°/2 mm.; yield 11 g.

1-Methyl-2-benzylpiperidine. A Grignard reaction was carried out in the usual manner using 34.2 g. of benzyl bromide, 4.8 g. of magnesium, and 22.6 g. of 1-methyl-2-piperidone. The product, 1-methyl-2-benzyl-1,4,5,6-tetrahydropyridine boiled at 120°/2 mm.; yield, 9 g.

The product of the above reaction was dissolved in 100 cc. of alcohol and hydrogenated at room temperature and atmospheric pressure in the presence of Adams' catalyst. 1-Methyl-2-benzylpiperidine was obtained as an oil, boiling at 105°/3 mm. A picrate, m.p. 181°, corr., obtained from this base corresponded in melting point to that of the same compound obtained by Bryans and Pyman (3) by the reduction of 2-benzylpyridine methosalts.

1-Methyl-2-(p-hydroxybenzyl)piperidine. Four grams of 1-methyl-2-benzylpiperidine was dissolved in 12 g. of concentrated sulfuric acid, cooled to −10°, and a mixture of 2.5 cc. of concentrated nitric acid dissolved in 6 g. of concentrated sulfuric acid was added dropwise to the solution with stirring. After standing for one hour at −10°, it was poured onto ice, basified, and the oil which separated was extracted with ether. After drying the ether, the solvent was removed and 4.7 g. of crude 1-methyl-2-(*p*-nitrobenzyl)piperidine was obtained. This was dissolved in 50 cc. of absolute alcohol and hydrogenated at room temperature and atmospheric pressure in the presence of Adams' platinum catalyst. This yielded 3 g. of 1-methyl-2-(*p*-aminobenzyl)piperidine boiling at 145°/4 mm.

Three grams of 1-methyl-2-(*p*-aminobenzyl)piperidine was dissolved in a mixture of 5 g. of concentrated sulfuric acid in 50 cc. of water. The solution was cooled to 2° and a solution of 1 g. of sodium nitrite in 10 cc. of water was added dropwise with stirring to the amine solution. It was then warmed on the steam-bath in the presence of copper until the evolution of nitrogen ceased. It was cooled, basified with sodium carbonate, and extracted with ether. After drying, the ether was removed and the residue crystallized from benzene. This yielded 1.8 g. of 1-methyl-2-(*p*-hydroxybenzyl)piperidine, melting at 153°.

1-Methyl-2-(p-dimethylcarbamoxybenzyl)piperidine hydrochloride. One and five-tenths gram of 1-methyl-2-(*p*-hydroxybenzyl)piperidine and 1 g. of dimethylcarbamyl chloride were dissolved in 10 cc. of dry pyridine and the solution heated on a steam-bath for three hours. The pyridine was then removed in vacuum, dilute alkali added to the residue, and the liberated base extracted with ether. This, on transformation to the hydrochloride in the usual manner and recrystallization from ethyl acetate, gave the dimethylcarbamyl ester, melting at 166°.

1-(p-Dimethylcarbamoxybenzyl)piperidine hydrochloride. *p*-Hydroxybenzylpiperidine was prepared according to the method of Königs and Bernhart (4). Four grams of N-*p*-hydroxybenzylpiperidine was dissolved in 12 cc. of pyridine and 3 g. of dimethylcarbamyl chloride added. The mixture was heated on the steam-bath for 4 hours and then the pyridine was distilled off in a vacuum, and the residue alkalized with dilute sodium hydroxide solution. The oil was extracted with ether and the ether distilled off. The residue was crystallized from Skellysolve B. The material was dissolved in ether and HCl gas bubbled in. The hydrochloride was crystallized from acetone, m.p. 205°; yield 3.8 g.

Anal. Calc'd for $C_{15}H_{22}N_2O_2 \cdot HCl$: N, 9.38. Found: N, 9.18.

SUMMARY

1. A series of 1-alkyl-2-arylpiperidines was prepared and some members were found to have a slight analgesic activity.

2. A series of 1-alkyl-2-benzyl piperidine derivatives was found to be without analgesic activity.

3. In both the above series the introduction of a 2-acyloxyl group resulted in compounds of no activity.

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[CONTRIBUTION NO. 103 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

PIPERIDINE DERIVATIVES. PART III. 4-ARYLPIPERIDINES[1]

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In a previous paper[2] the synthesis of 1-alkyl-2-aryl- and 1-alkyl-2-aralkylpiperidines from 1-alkyl-2-piperidones was described. Similar synthetic methods have been applied to 1-alkyl-4-piperidones to yield the isomeric 4-phenylpiperidines I. As in the case of the 1-methyl-2-benzylpiperidine, the 1-methyl-4-phenylpiperidine structure may be considered inherent in the morphine nucleus II and hence it or its derivatives might be expected to have analgesic activity. This approach to the synthesis of simpler structure with compounds of morphine-like activity is not new. Eisleb and Schaumann (1) have described piperidine compounds of the structure III (R = alkyl, R^1 = alkoxy, alkyl, etc.), one of the compounds (III, R = CH_3, R^1 = C_2H_5O) being clinically employed under the name of Demerol. Since the inception of the program of work described here, Jensen & Lundquist (2) have described compounds of the structure I (R = methyl, R^1 = acyloxy, R^2 = H). The compounds are stated to have an activity in the case of I (R = methyl, R^1 = propionoxy, R^2 = H) which is five to ten times that of Demerol. A British Patent recently issued (3) describes 1,2,2,6,6-pentamethyl-4-phenyl-4-acetoxypiperidine for which analgesic activity is claimed.

The synthetic scheme employed is shown in Figure 1.

The reaction of the arylmagnesium halide or lithiumaryl with 1-alkyl-4-piperidones yields the piperidinols VI. The corresponding 2-piperidones[2] invariably gave 1,4,5,6-tetrahydropyridines, spontaneous dehydration occurring during the isolation of the reaction product. The alcohols VI can be readily dehydrated to the corresponding 1-alkyl-4-aryl-1,2,5,6-tetrahydropyridines, IX, by means of the usual reagents, such as potassium acid sulfate, hydrobromic acid, and thionyl chloride. The tetrahydropyridines IX are readily hydrogenated either with nickel or noble metal catalysts to the saturated piperidines VIII. The piperidinols VI can be readily acylated with acid anhydrides in pyridine or anhydrides catalyzed by a trace of sulfuric or perchloric acid. With acyl chlorides in pyridine less satisfactory results were obtained, partial dehydration usually occurring. Jensen and Lundquist (2) state that they could not prepare certain esters, amongst them the phenylacetic ester. We found this to be prepared without difficulty using phenylacetic anhydride, and it is possible that the remaining esters mentioned by them as unobtainable may be prepared by the same method.

The lithium or magnesium compounds V can be also directly acylated by modification of the method of Houben (4). Yields in this case are of the same order as when the 2-step process is employed.

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[1] This paper was presented, in part, at the Medicinal Chemistry section of the Gibson Island Conferences of the A.A.A.S. 1946. Paper No. II, preceding article.

[2] Lee, Ziering, Heineman, and Berger, preceding paper.

Attempts to run the Grignard reaction with 1-butyl-4-piperidone and cyclohexylmagnesium chloride failed. The reagent apparently catalyzes on aldol condensation, with the formation of 1-butyl-4-(1′-butyl-4′-oxo-3′-piperidyl)-4hydroxypiperidine.

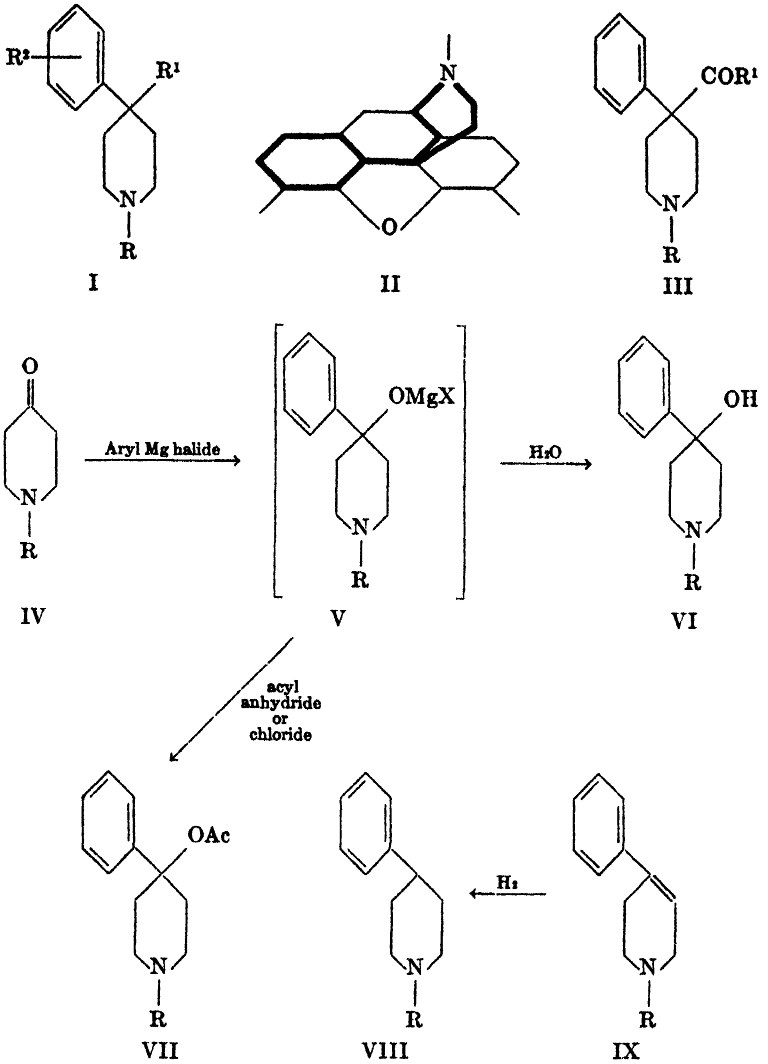

Fig. 1

The compounds obtained are shown in Tables I, II, III, and IV.

In the experimental part only those experiments which are typical of the pro-

TABLE I

1-Substituted 4-Aryl-4-hydroxypiperidines

SUBSTANCE: 4-HYDROXYPIPERIDINES	M.P., °C.*	B.P., °C.	FORMULA	M.W.	ANALYSIS Calculated C	ANALYSIS Calculated H	ANALYSIS Calculated N	ANALYSIS Found C	ANALYSIS Found H	ANALYSIS Found N
1-Allyl-4-phenyl-	86	135/2 mm.	$C_{14}H_{19}NO$	217.3	77.31	8.81		77.87	7.48	
1-Methyl-4-(*o*-methoxyphenyl)-	117–118 EtOAc	130/1 mm.	$C_{13}H_{19}NO_2$	221.3	70.53	8.65		70.4	8.5	
1-Methyl-4-(*m*-methoxyphenyl)-	112–113 EtOAc	162/3 mm.	$C_{13}H_{19}NO_2$	221.3	70.53	8.65		70.89	8.79	
1-Methyl-4-(*p*-methoxyphenyl)-	116	155/1 mm.	$C_{13}H_{19}NO_2$	221.3	70.53	8.65				
1-Ethyl-4-(*p*-methoxyphenyl)-	97	160/2 mm.	$C_{14}H_{21}NO_2$	235.3	71.44	8.99		71.83	9.09	
1-Butyl-4-(*p*-tolyl)-	87	155/2 mm.	$C_{16}H_{25}NO$	247.4	77.67	10.18		77.37	9.86	
1-Ethyl-4-phenyl-	87	143/1 mm.	$C_{13}H_{19}NO$	205.3	76.05	9.32		76.04	9.41	
1-Benzyl-4-phenyl-	103 base 216 (HCl)		$C_{18}H_{21}NO \cdot HCl$	303.8	71.16	6.96		71.60	6.68	
1-Butyl-4-phenyl-	86–88		$C_{15}H_{23}NO$	233.3	77.22	9.93		77.55	9.74	
1-Butyl-4-benzyl-	156–157		$C_{16}H_{26}ClNO$	283.9			4.94			5.02
1-Isopropyl-4-phenyl-	231 (HCl) 81	152/5 mm.	$C_{14}H_{21}NO \cdot HCl$	255.8	65.73	8.28		66.23	8.82	
1-Butyl-4-(*p*-methoxyphenyl)-	104		$C_{16}H_{25}NO_2$	263.4	72.95	9.57		72.90	9.20	
1-Methyl-4-phenyl-	111		$C_{12}H_{17}NO$	191.3	75.34	8.96		75.53	8.89	
1-Butyl-4-(*m*-tolyl)-	100		$C_{16}H_{25}NO$	247.4	77.67	10.18		77.59	9.92	
1-Butyl-4-[naphthyl-(1)]-	228–229(HBr) (corr)		$C_{19}H_{20}BrNO$	358.3	63.69	5.63		62.7	7.0	
1-Butyl-4-(1′-butyl-4′-oxo-3′-piperidyl)-dihydrochloride	188–190		$C_{18}H_{34}Cl_2N_2O_2$	381.4			7.35			7.06

* When not otherwise stated, bases crystallized from hexane and hydrochlorides from acetone. M.P.'s uncorrected.

TABLE II

1-ALKYL-4-SUBSTITUTED-4-PIPERIDINOL ESTERS

SUBSTANCE: PIPERIDINE HYDROCHLORIDE	M P, °C *	FORMULA	M W.	ANALYSIS					
				Calculated			Found		
				C	H	N	C	H	N
1-Propyl-4-phenyl-4-propionoxy-	218–219	$C_{17}H_{25}NO_2 \cdot HCl$	310.9	65.47	8.35		66.01	7.54	
1-Isopropyl-4-phenyl-4-propionoxy-	220–221	$C_{17}H_{25}NO_2 \cdot HCl$	310.9	65.47	8.35		65.66	8.51	
1-Allyl-4-phenyl-4-propionoxy-	190–191	$C_{17}H_{23}NO_2 \cdot HCl$	308.9	66.10	7.77		65.96	7.85	
1-Butyl-4-(*p*-tolyl)-4-propionoxy-	196–197	$C_{19}H_{29}NO_2 \cdot HCl$	340.9	66.94	8.86		67.49	8.78	
1-Ethyl-4-(*p*-methoxyphenyl)-4-propionoxy-	164–165	$C_{17}H_{25}NO_3 \cdot HCl$	328.9	62.09	7.91		62.12	7.85	
1-Methyl-4-phenyl-4-dimethylcarbamoxy-	179–180	$C_{15}H_{22}N_2O_2 \cdot HCl$	284.8	60.24	8.13		59.85	8.00	
1-Methyl-4-phenyl-4-acetoxy-	212–213	$C_{14}H_{19}NO_2 \cdot HCl$	269.8	62.32	7.47		62.42	7.45	
1-Butyl-4-phenyl-4-butyroxy-	206–207	$C_{19}H_{29}NO_2 \cdot HCl$	339.9	67.12	8.89		67.00	8.54	
1-Ethyl-4-phenyl-4-butyroxy-	209–210	$C_{17}H_{25}NO_2 \cdot HCl$	312.9	65.25	8.38		64.93	8.09	
1-Ethyl-4-phenyl-4-propionoxy-	194–195	$C_{16}H_{23}NO_2 \cdot HCl$	297.9	64.50	8.12		63.96	8.08	
1-Methyl-4-(*p*-methoxyphenyl)-4-propionoxy-	120–121	$C_{16}H_{23}NO_3 \cdot HCl$	313.9	61.23	7.71		61.20	7.76	
1-Methyl-4-phenyl-4-propionoxy-	182–183	$C_{15}H_{21}NO_2 \cdot HCl$	283.8	63.49	7.82		63.17	7.87	
1-Methyl-4-phenyl-4-butyroxy-	192–193	$C_{16}H_{23}NO_2 \cdot HCl$	297.9	64.50	8.12		64.47	7.81	
1-Benzyl-4-phenyl-4-propionoxy-	210–211	$C_{21}H_{25}NO_2 \cdot HCl$	359.9	70.08	7.28		70.50	6.65	
1-Butyl-4-phenyl-4-propionoxy-	205–206	$C_{18}H_{27}NO_2 \cdot HCl$	325.9	66.34	8.66		66.50	8.44	
1-Butyl-4-[naphthyl-(1)]-4-acetoxy-	223.5 (corr)	$C_{18}H_{28}ClNO_2$	361.9	69.69	7.80		69.7	7.44	
1-Butyl-4-[naphthyl-(1)]-4-propionoxy-	212–213	$C_{22}H_{30}ClNO_2$	375.9	70.28	8.04		70.0	7.9	
1-Methyl-4-phenyl-4-benzoyloxy-	214–215 acetone MeOH	$C_{19}H_{21}NO_2 \cdot HCl$	331 9	68.80	6.64	4.22	68.45	6.65	4.12
1-Butyl-4-phenyl-4-carbethoxyoxy-	173–174 EtOAc	$C_{18}H_{27}NO_3 \cdot HCl$	341.9	63.25	8.20	4.11	63.40	7.91	3.96
1-Methyl-4-phenyl-4-β,β-dimethylacroyloxy-	210–211	$C_{17}H_{23}NO_2 \cdot HCl$	309.9	65.90	7.76		66.13	7.53	
1-Butyl-4-phenyl-4-acetoxy-	207–208	$C_{17}H_{25}NO_2 \cdot HCl$	311.9	65.50	8.35	4.50	65.92	7.88	4.52
1-Butyl-4-phenyl-4-β-carbomethoxypropionoxy-	126–128 EtOAc	$C_{20}H_{29}NO_4 \cdot HCl$	383.9	62.60	7.80	3.65	62.86	7.80	3.87
1-Butyl-4-phenyl-4-ethoxyacetoxy-	202–204.5	$C_{19}H_{29}NO_3 \cdot HCl$	35[illegible].9	64.15	8.44	3.94	64.0[illegible]	8.[illegible]	4.14

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* When not otherwise stated crystallized from acetone.

cedures employed are described since otherwise the same methods were employed.

Pharmacological results. These will be described in detail in another place. The method of assay was substantially that of Ercoli and Lewis (5). Generally it may be said that the piperidinols VI showed only slight activity. The tetrahydropyridines IX showed distinct activity, for example, in the case of 1-ethyl-4-*p*-methoxyphenyl-1,2,5,6-tetrahydropyridine the activity was about $\frac{1}{30}$ of that of morphine. The saturated piperidines obtained by hydrogenation of these retained about the same activity, *p*-substitution still giving the highest activity, which was at its best with the more difficultly hydrolyzable acyloxy groups such as the *p*-dimethylcarbamoxy group.

TABLE III

1-ALKYL-4-PHENYL-1,2,5,6-TETRAHYDROPYRIDINE

SUBSTANCE TETRAHYDROPYRIDINE		M.P., °C.*	FORMULA	M.W.	ANALYSIS					
					Calculated			Found		
					C	H	N	C	H	N
1-Methyl-4-*o*-methoxyphenyl		b.p., oil 135/10 mm.	$C_{13}H_{17}NO$	203.3	76.8	8.43		76.05	8.2	
1-Methyl-4-*m*-hydroxyphenyl	HBr	195–198 EtOAc	$C_{12}H_{18}BrNO$	272.2	52.9	6.2	Br 27.4	52.8	5.8	Br 29.3
1-Methyl-4-*p*-methoxyphenyl-	HCl	178	$C_{13}H_{18}ClNO$	239.7			5.84			5.71
1-Methyl-4-phenyl-	HCl	241–243 (corr)	$C_{12}H_{16}ClN$	208.7	69.0	7.24		68.6	7.8	
1-Ethyl-4-*p*-methoxyphenyl-	HCl	198	$C_{14}H_{20}ClNO$	253.8	66.3	7.94		65.9	7.7	

* Unless otherwise stated, crystallized from acetone.

Acylation of the piperidinols VI to obtain the esters VII is accompanied by an increase in activity. The fatty acid esters show the best activity. The peak activity is obtained with the propionyl group. 1-Methyl-4-phenyl-4-propionoxypiperidine is as active in the test at a dose level of 1 mg. as 25 mg. of Demerol or 3 mg. of morphine. The corresponding acetyl compound is $\frac{1}{25}$ as active and the butyryl $\frac{1}{5}$ as active. The same order of activity for these three compounds was also found by Jensen & Lundquist (2).

Increase in the length of the alkyl chain at R in the compounds VII retaining the propionoxy group at position 4 results in a decrease of both activity and toxicity, the therapeutic ratio remaining approximately constant. Compounds with unbranched 1-alkyl chains are all unstable in water. However, if the residue in the 1-position is branched as, for example, in 1-isopropyl-4-phenyl-4-

TABLE IV

1-ALKYL-4-PHENYLPIPERIDINES

SUBSTANCE		M.P., °C.*	FORMULA	M W	ANALYSIS					
					Calculated			Found		
					C	H	N	C	H	N
1-Methyl-4-*o*-methoxyphenyl	HCl	240–242	$C_{13}H_{20}ClNO$	241.7	64.6	8.3		63.9	7.7	
1-Methyl-4-*o*-hydroxyphenyl	HBr	180–181 EtOAc	$C_{12}H_{18}BrNO$	272.2	52.9	6.7		52.3	6.7	
1-Methyl-4-*p*-hydroxyphenyl	HBr	210	$C_{12}H_{18}BrNO$	272.2	52.9	6.7		—	—	
1-Methyl-4-*m*-hydroxyphenyl	HBr	206	$C_{12}H_{18}BrNO$	272.2	52.9	6.7		53.1	6.3	
1-Ethyl-4-*p*-methoxyphenyl		b.p. 116/1 mm.	—	—	—	—		—	—	
1-Methyl-4-*o*-dimethylcarbamoxyphenyl	HCl	222	$C_{15}H_{23}ClN_2O_2$	298.8			9.37			9.41
1-Methyl-4-*m*-dimethylcarbamoxyphenyl	HCl	—	$C_{15}H_{23}ClN_2O_2$	298.8	60.3	7.7		60.0	7.66	
1-Methyl-4-*p*-dimethylcarbamoxyphenyl	HCl	246	$C_{15}H_{23}ClN_2O_2$	298.8			9.38			9.64
1-Ethyl-4-dimethylcarbamoxyphenyl	HCl	208	$C_{16}H_{25}ClN_2O_2$	312.8	61.4	8.05		61.8	7.5	

* Unless otherwise stated crystallized from acetone.

propionoxypiperidine, considerable stability is obtained. This compound can be kept at 40° in aqueous solution for months, whereas the corresponding 1-methyl compound is degraded very quickly.

Substitution in the phenyl nucleus of compounds VII gives material of lower activities. Methoxyl groups lower the activities to $\frac{1}{150}$ to $\frac{1}{200}$ of that of the unsubstituted compounds. With the methyl group as a substituent the dystherapeutic effect is less being least with the *m*-tolyl compound, here however the compound is only $\frac{1}{5}$ as active as the unsubstituted derivative.

In Stuart molecular models of compounds of the type of VII, where the propionoxy group occupies position 4, the acyloxy side chain is seen to simulate very closely the cyclohexane ring in models of the morphine skeleton. The oxygen of the CO group occupies a position almost identical with that of the ether-oxygen of morphine, and the two end-carbon atoms of the propionoxy group simulate positions of the carbon atoms 5 and 6 of morphine. In view of this and of the results in the 1-alkyl-4-phenyl-4-carbalkoxy (or 4 carbalkyl) series (III, R = alkyl, R^1 = alkyl or alkoxy) (1), it would appear that the minimal skeletal structure in the morphine molecule required for the high analgesic activity is represented by the 1-methyl-4-phenylpiperidine moiety, with the carbon atoms 5, 6, and 7 and the ether-oxygen atom.

Acknowledgment. The analysis of the compounds recorded here was performed in the Microanalytical Division of these Laboratories by Dr. Al Steyermark and his co-workers and the pharmacological results are due to Drs. R. H. K. Foster, N. Ercoli, and G. Lehmann and their co-workers of the Pharmacological Laboratory. We are glad to express our appreciation of their cooperation.

EXPERIMENTAL

1-Methyl-4-(p-methoxyphenyl)-4-hydroxypiperidine. To a three-necked flask provided with a ground sealed stirrer, dropping-funnel, and reflux condenser, was added 4.8 g. of magnesium and 150 cc. of dry ether. *p*-Bromoanisole (38 g.) in 50 cc. of dry ether was added dropwise to form the Grignard reagent in the usual manner. The ether solution was refluxed for one hour and to the reaction mixture, cooled in an ice-bath, 23 g. of 1-methyl-4-piperidone in 100 cc. of ether was added dropwise. After the addition, the mixture was refluxed for 8 hours, during which the gummy complex became solid. This was decomposed with 50 cc. of 20% hydrochloric acid. The ether layer was separated and the aqueous layer washed with ether. The aqueous layer was saturated with potassium carbonate and extracted with ether. The ether solution of the basic product was dried over sodium sulfate, and after removal of the ether, the residue was fractionated. 1-Methyl-4-hydroxy-4-*p*-methoxyphenylpiperidine boiled at 155° at 1 mm. It was crystallized from benzene and melted at 117–118°; yield 10 g.

1-Methyl-4-(p-methoxyphenyl)-1,2,5,6-tetrahydropyridine. 1-Methyl-4-hydroxy-4-*p*-methoxyphenylpiperidine (2.2 g.) was mixed with 2.7 g. of anhydrous potassium bisulfate and heated to 160° under vacuum at 10 mm. for 10 minutes. The flask was cooled, the contents dissolved in water and the solution saturated with potassium carbonate and extracted with ether, which was dried over potassium carbonate. After removal of the ether the 1-methyl-4-*p*-methoxyphenyl-1,2,5,6-tetrahydropyridine crystallized. It was recrystallized from Skellysolve B, m.p. 101°; yield 1 g. The hydrochloride melted at 178° uncorr.

1-Methyl-4-(p-methoxyphenyl)piperidine. 1-Methyl-4-*p*-methoxyphenyl-1,2,5,6-tetrahydropyridine (3.2 g.) was dissolved in 100 cc. of methanol and reduced in the presence of

5 g. of Raney nickel under a pressure of 50 lbs. of hydrogen at room temperature. The catalyst was filtered off and the alcohol was distilled off *in vacuo*. The residue was demethylated directly according to the procedure below.

1-Methyl-4-(p-hydroxyphenyl)piperidine. 1-Methyl-4-*p*-methoxyphenylpiperidine base (3 g.) was dissolved in a mixture of 15 cc. of acetic acid and 10 cc. of 48% hydrobromic acid. The mixture was refluxed for 4 hours. The acids were distilled off in vacuum and the residue was crystallized from alcohol, m.p. 210°; yield 3 g.

1-Methyl-4-p-(dimethylcarbamoxyphenyl)piperidine. 1-Methyl-4-*p*-hydroxyphenylpiperidine hydrobromide (20 g.) was dissolved in 100 cc. of water and the solution saturated with potassium carbonate. The separated piperidine base was dissolved in ether. The ether solution was dried and the ether removed by distillation. The free phenolic base was dissolved in 50 cc. of dry pyridine and 9 g. of dimethylcarbamyl chloride were added. After heating on a steam-bath for 3 hours, a further 9 g. of dimethylcarbamyl chloride was again added and the solution heated for another hour. The solvent was then removed *in vacuo* and the residue dissolved in water, and the solution made alkaline with sodium hydroxide. The dimethylcarbamyl ester was extracted with ether. HCl gas was bubbled in to precipitate the hydrochloride, which was then crystallized from acetone, m.p. 245–247°; yield 18 g.

1-Methyl-4-(m-hydroxyphenyl)-1,2,5,6-tetrahydropyridine. 1-Methyl-4-(*m*-methoxyphenyl)-4-hydroxy piperidine (1 g.) was dissolved in 15 cc. of glacial acetic acid, 5 cc. of 48% hydrobromic acid was added, and the mixture was refluxed for 15 minutes. The acids were removed under vacuum and the pink residue dissolved in alcohol and crystallized by the addition of ethyl acetate; yield, 200 mg. of 1-methyl-4-(*m*-hydroxyphenyl)-1,2,5,6-tetrahydropyridine, m.p. 194–196°.

1-Isopropyl-4-piperidone. Isopropylamine (684 cc.) was dissolved in 1600 cc. of absolute alcohol and to the solution, cooled in an ice-bath, 2800 cc. of ethyl acrylate was added portionwise. The resulting solution was kept for 1 week at room temperature and then worked up in the usual manner (6). The di-(β-carbethoxyethyl)isopropylamine (7) distilled at 128°/2mm.; yield 1600 g.

In a 3-necked, 5-liter, round-bottom flask provided with a Hershberg stirrer, dropping-funnel and reflux condenser, 46 g. of sodium was powdered under 1000 cc. of dry toluene. The inside temperature was brought to 90° with an oil-bath, and 518 g. of di-(β-carbethoxyethyl)isopropylamine was added dropwise with stirring. As the condensation progressed the sodium salt of 1-isopropyl-3-carbethoxy-4-piperidone precipitated out. When the addition was complete the mixture was heated and stirred at 90° for 3 hours longer. The contents were cooled, 1000 cc. of water added, the toluene was separated, and the aqueous layer was acidified with 480 cc. of concentrated hydrochloric acid. The solution of 1-isopropyl-3-carbethoxy-4-piperidone hydrochloride was refluxed until a drop of the solution gave only a faint color with ferric chloride. Most of the water was removed in vacuum and the residue made alkaline with 50% sodium hydroxide solution to about *p*H 11 The mixture was then extracted with ether. The ether solution was dried over potassium carbonate and the ether removed. The residual oil on fractionation yielded 135 g. of 1-isopropyl-4-piperidone, b.p. 103°/25 mm.

1-Isobutyl-4-piperidone. Ethyl acrylate (1600 cc.) was added in portions to a cooled solution of 365 g. of isobutylamine in 500 cc. of alcohol. The resulting solution was kept for seven days at room temperature, the alcohol and excess ethyl acrylate were distilled off in vac. and the residue distilled in vac., b.p. 130°/1 mm.; yield 1062 g.

The above di-ester (546 g.) was cyclized with 46 g. of sodium shot in 1300 cc. of toluene. As the condensation proceeded the sodium salt of the keto ester separated out. The reaction product was worked up as above to yield 191 g. of 1-isobutyl-4-piperidone, b.p. 105°/22 mm.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.68; H, 10.98.
Found: C, 69.57; H, 11.28.

1-sec.-Butyl-4-piperidone. In a similar manner to that described above, 507 cc. of *sec.*-

butylamine, 500 cc. of alcohol, and 1087 cc. of ethyl acrylate yielded 400 g. of di-(β-carbethoxyethyl)-*sec.*-butylamine, b.p. 144°/2 mm. (7). The di-ester (400 g.) cyclized in a similar manner with 34.5 g. of sodium yielded, after hydrolysis with hydrochloric acid, 150 g. of 1-*sec.*-butyl-4-piperidone, b.p. 112°/23 mm.

Anal. Calc'd for $C_9H_{17}NO$: C, 69.68; H, 10.98.
Found: C, 69.26; H, 11.17.

1-Butyl-4-phenyl-4-hydroxypiperidine. The Grignard reaction was carried out with 3.6 g. of magnesium and 23.5 g. of bromobenzene in the usual manner. The flask was cooled in an ice-bath and 15.5 g. of 1-butylpiperidone-4 was added dropwise. On working up in the usual manner, 8 g. of 1-butyl-4-phenyl-4-hydroxypiperidine was obtained. After crystallization from Skellysolve B, the compound melted at 86–88°.

Alternate synthesis. Phenyllithium was prepared in the usual manner from 2.1 g. of lithium wire, 200 cc. of ether and 23.6 g. of bromobenzene. The reaction flask was kept under dry nitrogen throughout the reaction. The flask was cooled to −20° and 15.5 g. of 1-butyl-4-piperidone in 45 cc. of ether was slowly added. The reaction mixture was stirred for 2 hours at room temperature and finally decomposed with ice and 18% hydrochloric acid. An insoluble salt separated which was brought into solution with water. The ether solution was separated and discarded, after being extracted with dilute hydrochloric acid. The acid solutions were combined and alkalized with 50% NaOH solution to *p*H 10. A crystalline base separated which was filtered off. The aqueous solution was extracted with ether and the ether solution dried and evaporated to yield a further crop of crystals. The 1-butyl-4-phenyl-4-hydroxypiperidine was recrystallized from Skellysolve B, melted at 86–88°; yield 17 g.

Propionate. 1-Butyl-4-phenyl-4-hydroxypiperidine (1 g.) was dissolved in 10 cc. of propionic anhydride and 1 drop of conc'd sulfuric acid added. The mixture was heated on a steam-bath for 3 hours, and the excess propionic anhydride removed in vacuum. The residue was taken up in water and alkalized with sodium carbonate. The oil was extracted with ether and after drying over potassium carbonate, HCl gas was bubbled in. The hydrochloride was crystallized from acetone, m.p. 204–206°.

Methiodide. 1-Butyl-4-phenyl-4-propionoxypiperidine (2 g.) was dissolved in excess methyl iodide. An oil started to precipitate in a few minutes. After standing overnight ether was added and the oil crystallized. The product was recrystallized from ethyl acetate-methanol mixture and melted at 160–165°.

Anal. Calc'd for $C_{19}H_{30}INO_2$: C, 52.90; H, 6.96.
Found: C, 53.27; H, 6.74.

N-oxide. 1-Butyl-4-phenyl-4-propionoxypiperidine (5 g.) was dissolved in 100 cc. of chloroform and 2.3 g. of perbenzoic acid in 40 cc. of chloroform added. After standing overnight in the ice-box the chloroform was distilled off in vacuum and the residue dissolved in ether. HCl gas was bubbled into the ether solution to precipitate the hydrochloride, which was crystallized from acetone, m.p. 155–157°.

Anal. Calc'd for $C_{18}H_{27}NO_3 \cdot HCl$: C, 63.25; H, 8.20.
Found: C, 63.01; H, 8.13.

1-Isopropyl-4-phenyl-4-acetoxypiperidine hydrochloride by direct acylation of the lithium complex. Phenyllithium was prepared from 8.4 g. of lithium wire and 100 g. of bromobenzene in ether in the usual manner. The mixture was cooled with ice-water and 52 g. of 1-isopropyl-4-piperidone in dry benzene was added. The reaction mixture was refluxed for 1½ hours, the apparatus was arranged for distillation, and the ether distilled off until the temperature of the distillate reached 55–60°. One hundred cc. of additional benzene was added. The reaction was cooled to 5° with ice and water, and 100 cc. of acetic anhydride in 200 cc. of dry benzene was added. A yellow-green precipitate formed. At the end of the addition the entire reaction mass was thick and yellow-green in appearance. The reaction mass was diluted with 1 liter of dry benzene and the cooling bath removed and the reaction mixture brought to reflux temperature slowly. It was refluxed for 30 minutes and left to stand overnight. The next morning the entire mass was almost solid. Cooled with ice-water, it was decomposed with 100 cc. of ice-water, and finally 100 cc. of concentrated HCl with ice was added. A very insoluble hydrochloride precipitated. This was dissolved in about 4 liters of water and extracted with ether. The ether extract was discarded. The aqueous solution was basified with cooling to *p*H 10 and extracted with ether. The ether solution was dried over sodium sulfate overnight, filtered, concentrated to dryness, and fractionated through a small Vigreux column at 3 mm. Six grams of forerun boiling at 86–150° was obtained. The product distilled at 151° (3 mm.); yield 52.5 g. (55% of theory). On standing, the basic product obtained crystallized spontaneously. It was recrystallized from ligroin (30–60°), and melted at 75–76°. The base obtained was converted to the hydrochloride and recrystallized from acetone and methanol to yield the colorless crystalline 1-isopropyl-4-phenyl-4-acetoxypiperidine hydrochloride, m.p. 205–206°.

Anal. Calc'd for $C_{16}H_{23}NO_2 \cdot HCl$ (297.5): C, 64.55; H, 8.07.
Found: C, 64.62; H, 7.96.

The corresponding 4-propionoxy derivative prepared in a similar manner was obtained in 40% yield. 1-Isopropyl-4-phenyl-4-propionoxy piperidine hydrochloride was crystallized from acetone and melted at 212–213°.

Anal. Calc'd for $C_{17}H_{25}NO_2 \cdot HCl$ (311.5): C, 65.50; H, 8.35; N, 4.50.
Found: C, 65.35; H, 8.40; N, 4.51.

1-Butyl-4-cyclohexylpiperidine hydrochloride. 1-Butyl-4-phenyl-4-propionoxypiperidine hydrochloride (5 g.) was added to 100 cc. of ethanol containing 5 g. of PtO_2. The mixture was hydrogenated at 50 lbs. pressure at 80° until no more hydrogen was taken up. The mixture was filtered and the alcohol distilled off in vacuum. The residue was crystallized from acetone and melted at 240°.

Anal. Calc'd for $C_{23}H_{29}NO_2 \cdot HCl$: C, 71.23; H, 7.75; N, 3.61.
Found: C, 71.35; H, 7.34, N, 3.57.

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PIPERIDINE DERIVATIVES. IV. 4-ALKYL-, 4-CYCLOALKYL-, AND 4-HETEROCYCLYL-PIPERIDINES[1]

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In a previous paper of this series it was shown that certain members of the series of 1-alkyl-4-phenyl-4-acyloxypiperidines possess extremely high analgesic activity in rats when tested by a modification of the Hardy-Wolff-Goodell technique (1). Considerable variation of the alkyl and acyl substituents and of substitution in the phenyl nucleus was made, the optimum activity being found in compounds having an unsubstituted phenyl group at the 4-position. It was therefore thought desirable to find out whether the phenyl group could be replaced by other groups with the retention of analgesic activity. In this paper the synthesis of 4-heterocyclylpiperidines derived from pyridine, thiophene, and furan, the 4-heterocyclylalkylpiperidines derived from α-picoline and $\alpha\alpha'$-lutidine and the 4-methyl-, butyl-, and *n*-hexyl-piperidines and 4-cyclohexylpiperidines is reported.

The synthesis of the 1,4-dialkyl-4-hydroxypiperidines offered no difficulties. 1-Alkyl-4-piperidones I react with lithiumalkyls to yield the 1,4-dialkyl-4-hydroxy-piperidines (VII, R^1 = alkyl). Similarly, the heterocyclyllithium and heterocyclylalkyllithium compounds yielded the corresponding 4-piperidinols (VII, R^1 = 2-pyridyl, 3-pyridyl, 2-furyl, 2-picolyl, 2-lutidyl, and 2-thienyl). 1-Alkyl-4-piperidones with cycloalkylmagnesium halides gave no isolable yield of the desired 4-cyclohexyl derivative. The Grignard reagent in the reaction apparently catalyzes an aldol condensation of the 1-alkyl-4-piperidone to a compound of the type II. In the reaction of cyclohexylmagnesium chloride and 1-butyl-4-piperidone, a compound which analyzes correctly for 1-butyl-4-hydroxy-4 (1′-butyl-4′-keto-3′-piperidyl)piperidone hydrochloride (II, R = C_4H_9) was obtained. A similar reaction had already been noted in the corresponding reaction with 1-alkyl-2-piperidones (2). It was found that 4-phenyl-4-hydroxypiperidine salts III could be hydrogenated to the corresponding cyclohexyl compounds IV. The free bases could not be hydrogenated in this manner, neutral or acid conditions being required. The corresponding piperidinol esters V could not be hydrogenated to the 1-alkyl-4-cyclohexyl-4-piperidinol esters, in this case reduction occurs with removal of a molecule of acid and the formation of 1-alkyl-4-cycloalkylpiperidines VI.

Pharmacological results. The replacement of the phenyl group in 1-alkyl-4-phenyl-4-acyloxypiperidines as described here leads invariably to compounds of lowered activity. Replacing phenyl with a methyl or hexyl group gave compounds of practically no activity. The butyl group showed some slight activity.

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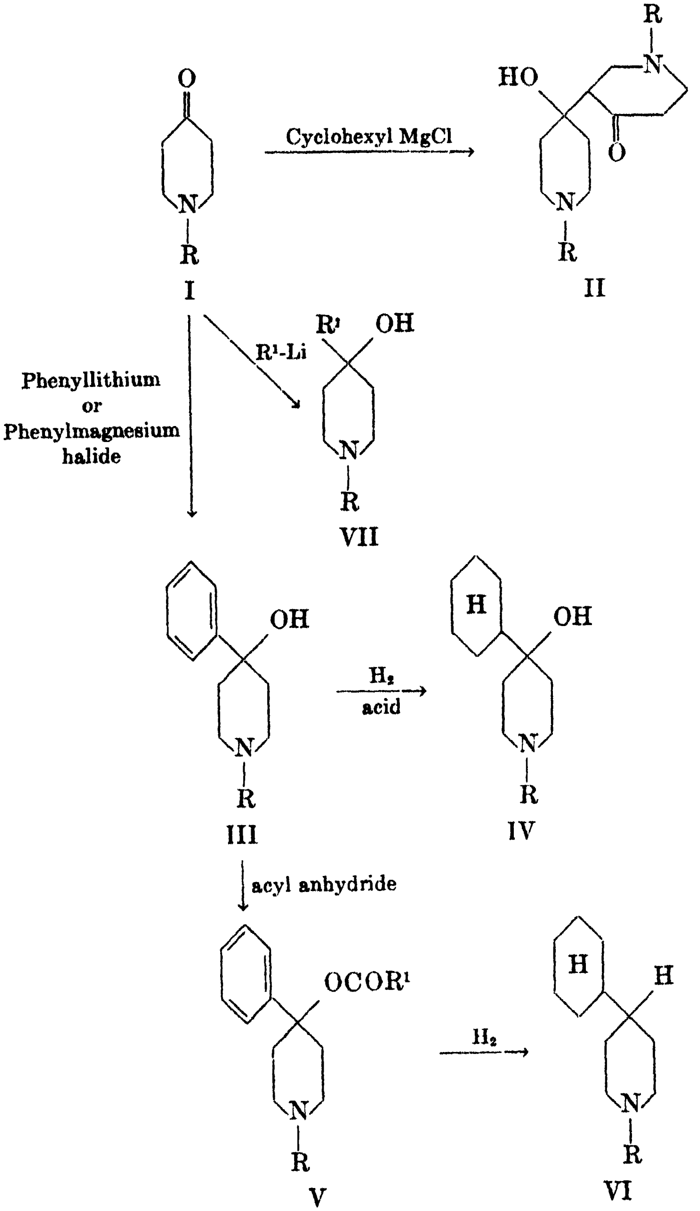
The acetate of 1,4-dibutyl-4-piperidinol was slightly active, the propionate and butyrate being of greater and about equal activity. This contrasts with the



4-phenyl series VI, where there is a pronounced peak of activity with the propionic ester. Replacing the phenyl residue in V with hydrogen as in the case of 1-butyl-4-propionoxypiperidine gives a compound which still has activity at higher dose levels.

The substitution of the phenyl in V with heterocyclyl or heterocyclylalkyl residues has a definite dystherapeutic effect. The best compound of this series is the β-pyridyl derivative. This compound has about half of the activity of Demerol and about half of the toxicity of the latter, but this activity is only about one-thirtieth of that of the corresponding phenyl compound. The substitution of phenyl by cyclohexyl in V, yielding the esters of IV, gives compounds which are also less active than the phenyl compounds. 1-Methyl-4-cyclohexyl-4-propionoxypiperidine has about one-third of the activity of 1-methyl-4-phenyl-4-propionoxypiperidine. It is, however, less toxic, and contrary to the latter, forms aqueous solutions which are stable under practical conditions. The compounds prepared are shown in Table I. Typical methods of preparation are given in the experimental part.

Acknowledgment. The analysis of the compounds recorded here was performed in the Microanalytical Division of these Laboratories by Dr. Al Steyermark and his co-workers and the pharmacological results are due to Drs. R. H. K. Foster, G. Lehmann, and their co-workers of the Pharmacological Laboratory. We wish to express our appreciation of their co-operation.

EXPERIMENTAL

4-(3-Pyridyl)-4-hydroxyl-1-butylpiperidine. Thirty-nine grams of butyl chloride in 250 cc. of dry ether was refluxed with 6 g. of lithium wire. The butyllithium solution which formed was cooled to −40° and 50 g. of 3-bromopyridine in 50 cc. of dry ether was added dropwise (3). An instantaneous reaction occurred, forming a brown complex, which was stirred at −40° for 15 minutes. Fifteen and one-half grams of 1-butyl-4-piperidone in 25 cc. of dry ether was slowly added at this temperature and on completion of the addition, the temperature was allowed to rise to −15°. After stirring for 45 minutes at this temperature the reaction mixture was decomposed by pouring it onto a mixture of ice and hydrochloric acid. The ethereal solution was separated, extracted with a little dilute hydrochloric acid and the acid solution returned to the reaction mixture. This was basified with cold 10% NaOH solution to *p*H 10 and extracted with ether. After drying the ether extract and removal of the solvent, 9 g. of a viscous yellow syrup remained which distilled at 156–158° at 0.5 mm. The product crystallized spontaneously and was recrystallized from hexane yielding 4-(3-pyridyl)-4-hydroxy-1-butylpiperidine, m.p. 80–81°.

The *acetate* was prepared by heating with acetic anhydride in the presence of a trace of sulfuric acid. The hydrochloride, when recrystallized from ethyl acetate-methanol, melted at 215–216°. The *propionate* hydrochloride prepared under the same conditions melts 198–199°.

4-(2-Picolyl)-4-hydroxy-1-butylpiperidine. Picolyllithium was prepared from 28 g. of bromobenzene, 2.5 g. of lithium, and 12.4 g. of α-picoline as described by Bergmann and Rosenthal (4). The resultant picolyllithium was reacted with 15.5 g. of 1-butylpiperidone-4 under the conditions described above. On working up the reaction in the usual manner, 18.4 g. (75% yield) of a light thin syrup was obtained which boiled at 148–150°/0.9 mm.

The *acetate* prepared under the usual conditions is a hygroscopic amorphous glass. The *propionate* has similar characteristics.

4-Hydroxy-4-(6′-methyl-2′-pyridylmethyl)-1-butylpiperidine dihydrochloride. Phenyllithium was prepared in the usual manner from 5.0 g. of lithium and 49 g. of bromobenzene in 200 cc. of ether. To this, at 0°, 13.4 g. of 2,6-lutidine in ether was added in 20 minutes. The purplish-colored solution was cooled to −30° and 31 g. of 1-butyl-4-piperidone in 50 cc. of ether was added slowly. The color changed from purple to deep Burgundy-red and became clear. After a further ½ hour at −20° the reaction mixture was decomposed with a mixture of equal parts of concentrated hydrochloric acid and ice. The aqueous solution was separated and alkalinized, and extracted with ether. The ether solution was dried over potassium carbonate for 24 hours, filtered, and the solvent removed. The residue, fractionated at 1 mm., yielded 14.4 g. of material boiling at 141–142° and analyzed correctly for the above-mentioned structure.

The *dihydrochloride* is a light yellow hygroscopic amorphous compound containing 3 molecules of water of crystallization. The *acetate* and *propionate* are hygroscopic glasses.

4-Methyl-4-hydroxy-1-butylpiperidine. Twenty-eight grams of freshly distilled methyl iodide and 2.8 g. of freshly cut lithium metal were stirred in 200 cc. of ether. The reaction was complete in two hours. The mixture was cooled to −15° and 15.5 g. of 1-butylpiperidone-4 in ether was added dropwise. After stirring for one hour at this temperature, the mixture was decomposed with ice and hydrochloric acid and worked up in the usual manner. The reaction product, fractionated at 1.0 mm., yielded 12 g. of an oil boiling at 75–76°. The product is the desired 4-methyl-4-hydroxy-1-butylpiperidine.

4-Cyclohexyl-4-hydroxy-1-butylpiperidine hydrochloride. Eight grams of 1-butyl-4-phenyl-4-hydroxypiperidine hydrochloride was dissolved in 100 cc. of absolute alcohol and hydrogenated in the presence of Adams' platinum oxide catalyst at 85° and at a hydrogen pressure of 1100 lb./per sq. inch. The absorption of the theoretical amount of H_2 required four hours. The alcoholic solution was filtered, evaporated to dryness and the residue recrystallized from acetone. The hydrochloride melts at 223.5–225.5°. The *base* on crystallization from *n*-hexane melts at 96–98°. The acyloxy compounds were prepared by heating the bases with the respective acyl anhydrides in the presence of a drop of conc'd H_2SO_4 on a steam-bath. They were converted to the hydrochlorides and crystallized from ethyl acetate-methanol.

The *acetate hydrochloride* melts at 229–230°

The *propionate hydrochloride* melts at 224–225°.

The *butyrate hydrochloride* melts at 202.5°.

1-Butyl-4-hydroxy-4-(1′-butyl-4′-keto-3′-piperidyl)piperidine dihydrochloride. To a suspension of 3.3 g. of magnesium in 50 cc. of dry ether was added 16 g. of freshly distilled cyclohexyl chloride. Upon completion of the reaction the Grignard complex was heated for two hours more at reflux temperature. The reaction mixture was cooled to 0° and 15.5 g. of 1-butylpiperidone-4 in 25 cc. of dry ether was added. Upon completion of the addition, a white insoluble complex precipitated out. The reaction mixture was refluxed for 3 hours more and left to stand overnight. Decomposed and worked up in the usual manner, the basic fractions were collected in ether, the ether solution dried over Na_2SO_4, the solvent removed and the residual oil fractionated. Two fractions were obtained. At 9 mm., 5 g. of the starting piperidone boiling at 85–90° was recovered. The main fraction (8.5 g.) boiled at 140° at 0.25 mm. The higher-boiling fraction was converted to the hydrochloride and the crude hydrochloride was recrystallized from ethyl acetate and methanol with some ethyl ether. A colorless crystalline salt was obtained melting at 195–196°. It analyzed correctly for the piperidone aldol condensation product.

4-(2-Thienyl)-4-hydroxy-1-butylpiperidine. Fifty-two and one-half grams of dry bromobenzene was treated with 5 g. of lithium in 500 cc. of dry ether. Upon completion of the reaction the solution of phenyllithium was cooled to room temperature and 21 g. of dry freshly distilled thiophene in 25 cc. of dry ether was added rapidly, and the reaction mixture was refluxed for 2–3 hours. The solution was cooled to −20° and 15.5 g. of 1-butylpiperidone-4 was added. The solution was stirred at 25° for 1 hour and left to stand overnight. The reaction mixture was decomposed with ice and conc'd HCl and worked up in the usual manner. There was obtained a crystalline base which melted at 82–83° when recrystallized twice from Skellysolve B. The base was dissolved in dry ether and converted to the hydrochloride with dry HCl gas. The crystalline product obtained was recrystallized from a mixture of acetone and methanol to yield a colorless crystalline product melting at 168–

TABLE I

4,4-DISUBSTITUTED 1-BUTYLPIPERIDINES

1-BUTYLPIPERIDINE·HCl	M.P.* °C. AND SOLVENT OF CRYST.	FORMULA	ANALYSES					
			Calculated			Found		
			C	H	N	C	H	N
4-Butyl-4-hydroxy	147–148 (EtAc-MeOH)	$C_{13}H_{27}NO \cdot HCl$ (249.5)	62.55	11.21	5.62	62.58	11.16	5.52
4-Butyl-4-acetoxy	229–230 (EtAc-MeOH)	$C_{15}H_{29}NO_2 \cdot HCl$ (291.5)	61.75	10.30		61.42	10.27	
4-Butyl-4-propionoxy	218–219 (EtAc-MeOH)	$C_{16}H_{31}NO_2 \cdot HCl \cdot 1\ H_2O$ (323.5)	59.35	10.50		59.08	10.67	
4-Butyl-4-butyroxy	214–215 (EtAc-MeOH)	$C_{17}H_{33}NO_2 \cdot HCl$(319.5)	63.85	10.64		64.04	10.74	
4-(3-Pyridyl)-4-acetoxy HCl	215–216 (EtAc-MeOH)	$C_{16}H_{24}N_2O_2 \cdot 2HCl \cdot 0\ 5H_2O$ (358)	53.62	7.54		53.76	7.26	
4-(3-Pyridyl)-4-propionoxy HCl	198–199 (EtAc-MeOH)	$C_{17}H_{26}N_2O_2 \cdot 2HCl \cdot 0.3H_2O$	55.25	7.78		55.49	8.03	
4-(3-Pyridyl)-4-butyroxy HCl	154–155 (EtAc-MeOH)	$C_{18}H_{28}N_2O_2 \cdot 2HCl$ (377)			7.43			7.10
4-(2-Picolyl)-4-hydroxy HCl	glass	$C_{15}H_{24}N_2O \cdot 2HCl \cdot 0.5H_2O$ (330)	54.75	8.18		54.66	8.45	
4-(2-Picolyl)-4-acetoxy HCl	glass	$C_{17}H_{26}N_2O_2 \cdot 2HCl \cdot 1.5H_2O$ (390)	52.30	7.95	7.18	52.40	7.91	6.69
4-(2-Picolyl)-4-propionoxy·HCl	glass	$C_{18}H_{28}N_2O_2 \cdot 2HCl$ (377)	57.30	7.96		57.46	8.33	
4-Hydroxy-4-(1′-butyl-4′-keto-3′-piperidyl) HCl	195–196 (EtAc-MeOH-Et₂O)	$C_{18}H_{34}N_2O_2 \cdot 2HCl$ (383)	56.40	9.40	7.31	56.72	9.29	7.28
4-Propionoxy-4-(1′-butyl-4′-keto-3′-piperidyl)·HCl	syrup	$C_{21}H_{38}N_2O_3 \cdot 2HCl \cdot 3H_2O$ (493)	51.10	9.34	5.68	51.26	8.97	5.79
4-Hydroxy-4-(6′-methyl-2′-picolyl) HCl	amorphous powder	$C_{16}H_{26}N_2O \cdot 2HCl \cdot 3H_2O$ (389)			7.20			7.35
4-Acetoxy-4-(6′-methyl 2′-picolyl) HCl	glass	$C_{18}H_{28}N_2O_2 \cdot 2HCl \cdot 0.9H_2O$ (393.2)	54.95	8.08		55.06	8.05	
4-Propionoxy-4-(6′-methyl 2′-picolyl) HCl	glass	$C_{19}H_{30}N_2O_2 \cdot 2HCl \cdot 1.3H_2O$ (415)	54.95	8.34		55.01	8.58	
4-(2-Furyl)-4-hydroxy	glass	$C_{13}H_{21}NO_2 \cdot HCl$ (259.5)	60.15	8.48	5.40	60.04	8.78	5.44
4-(2-Furyl)-4-propionoxy	glass	$C_{16}H_{25}NO_3 \cdot HCl$ (315.5)			4.44			4.50
4-Cyclohexyl-4-hydroxy	223–225 (acetone)	$C_{15}H_{29}NO \cdot HCl$ (275.5)	62.25	10.89	5.08	65.45	10.81	4.99
4-Cyclohexyl-4-acetoxy	229–230 (EtAc-MeOH)	$C_{17}H_{31}NO_2 \cdot HCl$ (317.5)	64.25	10.06		64.31	9.54	
4-Cyclohexyl-4-propionoxy	224–225 (EtAc-MeOH)	$C_{18}H_{33}NO_2 \cdot HCl$ (331.5)	65.18	10.25	4.22	64.98	9.88	4.04

4-(2-Pyridyl)-4-hydroxy base	145–147/1 mm.	$C_{14}H_{22}N_2O$ (234)	71.81	9.40		71.94	9.07	
4-(2-Pyridyl)-4-propionoxy HCl	170–172 (EtAc-MeOH)	$C_{17}H_{26}N_2O_2\cdot 2HCl$			7.71			8.02
4-Methyl-4-hydroxy base	75–75/1 mm.	$C_{10}H_{21}NO\cdot 0.5H_2O$ (180)	66.70	12.20		66.64	11.99	
4-Methyl-4-propionoxy	226–228 (EtAc-MeOH)	$C_{13}H_{25}NO_2\cdot HCl$ (263.5)	59.20	9.87		59.10	9.68	
4-(2-Pyridylmethyl)-4-hydroxy dimethiodide	95–97 (alcohol)	$C_{17}H_{30}I_2N_2O\cdot 0.5\ H_2O$ (541)	37.70	5.73	5.18	37.59	5.79	4.87
4-Hexyl-4-propionoxy	210–211 (EtAc-MeOH)	$C_{18}H_{35}NO_2\cdot HCl\cdot 0.3H_2O$ (339.5)	63.60	10.78	4.12	63.67	10.57	3.88
4-Cyclohexyl-4-butyroxy	202.5 (EtAc)	$C_{19}H_{35}NO_2\cdot HCl$ (345.5)			4.10			4.60
4-(2-Thienyl)-4-hydroxy	168–169.5 (Acetone MeOH)	$C_{13}H_{21}NOS\cdot HCl$ (275.5)	56.62	7.90		56.72	7.81	
4-(2-Thienyl)-4-propionoxy	151–153 (EtAc-MeOH)	$C_{16}H_{25}NO_2S\cdot HCl$ (331.5)	57.95	7.82		57.90	7.92	

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* All melting points uncorrected.

169.5°. The product was the desired 4-(2-thienyl)-4-hydroxy-1-butylpiperidine hydrochloride.

The *propionate* of the above thienyl compound was prepared from the base with propionic anhydride and a catalytic amount of conc'd H_2SO_4 on the steam-bath. The product obtained was recrystallized from a mixture of ethyl acetate and methanol to yield colorless crystals of the desired propionate melting at 151–153°.

SUMMARY

1. A series of 4-alkyl-, 4-cycloalkyl-, 4-heterocyclyl-, and 4-heterocyclylalkyl-4-acyloxy-1-alkylpiperidines were prepared and tested for morphine-like analgesic activity.

2. Most of the members of the 4-alkyl-, 4-heterocyclyl- and 4-heterocyclylalkyl-piperidinol esters were inactive or slightly active at best. The most potent member of this series was one-half as active as Demerol.

3. The 4-cyclohexyl-4-piperidinol esters were the most active compounds in this series. Some members of this series are several times as active as Demerol.

4. Replacement of the phenyl group in 1-alkyl-4-phenyl-4-acyloxypiperidines with alkyl, heterocyclyl, heterocyclylalkyl, or cycloalkyl residues has a dystherapeutic effect.

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PIPERIDINE DERIVATIVES. V. 1,3-DIALKYL-4-ARYL-4-ACYLOXYPIPERIDINES

ALBERT ZIERING and JOHN LEE

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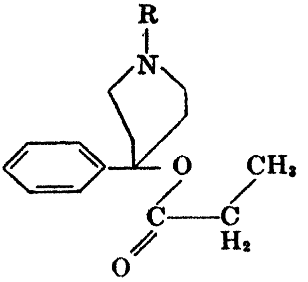
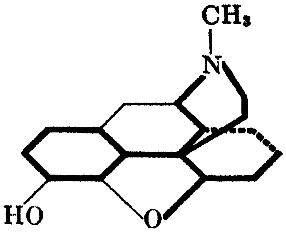
In a previous paper (1) it was shown that 1-alkyl-4-phenyl-4-propionoxypiperidines of the structure I which simulate, in part, that part of the dihydrodesoxymorphine-D structure II which is shown with heavy solid lines, have a high analgesic potency, which, although in some instances exceeding that of morphine, does not reach that of dihydrodesoxymorphine-D. This latter has been shown to be 5 to 10 times as active as morphine (2). It could therefore be reversely postulated that the fragment of dihydrodesoxymorphine-D structure responsible for its high activity is that indicated by the heavy solid and possibly the broken lines in II. It therefore became of interest to determine to what extent the remaining parts of the cyclohexane ring in II not simulated by the structure I, that is, the structure denoted by the broken lines, contributes to the analgesic effect of II.



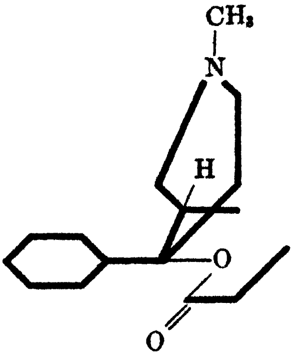
I



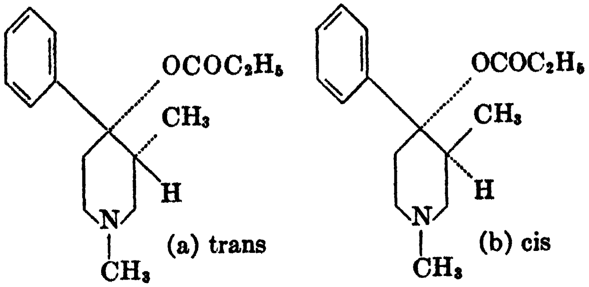
II

We have previously shown (3) that the substitution of the 4-propionoxy residue by 4-acetoxy residue in the structure I lowers the activity to about $\frac{1}{25}$ whilst the substitution of the higher member of the series, namely, the butyroxy residue reduces the activity to $\frac{1}{5}$ of the original. Maintaining this optimal substitution of the propionoxy residue in the structure I, a methyl group has been introduced in the position-3 of the piperidine nucleus yielding two compounds corresponding to the structures IVa and IVb, one of which (IVa) would be spatially related to dihydrodesoxymorphine-D as shown by the heavy print in the structure V. It might be expected that one of the isomers IVa or b might show increased activity whilst the other might be expected to substantially retain the order of activity of the compounds of structure I. This is found to be the case.

By the reaction of phenyllithium on 1,3-dimethyl-4-piperidone a mixture of diastereomeric alcohols was obtained. Fractional crystallization from Skellysolve B did not effect a separation, but in one instance, on letting the crude



V



(a) trans

(b) cis

IV

liquid residue (as obtained by decomposing the reaction mixture with water, separating the ether layer and distilling off the ether) stand at room temperature for a few days, the α form, m.p. 103° crystallized out. The filtrate was distilled in vacuum to yield a mixture of the α and β forms m.p. 72–85°. The α isomer yielded *dl*-α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 214–215°, whilst the mixed alcohols yielded a mixture of propionate hydrochlorides which could be fractionated into the above mentioned *dl*-α-propionate hydrochloride, m.p. 214–215° (Prep. Nu- 1196)[1] and a lower-melting *dl*-β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 190–192° (Prep. Nu-1779).

Resolution of the *dl*-α-ester was attempted with *d*-tartaric acid. Resolution did not take place because the readily crystallizable diastereo compound, the *dl*-α-ester-*d*-acid tartrate, formed immediately.

The *dl*-β-ester on treatment with *d*-tartaric acid yielded two acid tartrate monohydrates, one melting at 163–165° (Prep. Nu-1831) and the other melting in a range from 95–103° (Prep. Nu-1832). On treatment with *l*-malic acid, the *dl*-β-ester also yielded two acid malates, one melting at 134–135° and the other melting at 114–115°. No configuration has been assigned to these salts since the optical rotation of the hydrochlorides which can be derived from them is in all cases inappreciable. The rotation of the tartrates and malates must be ascribed entirely to the anion in each case, since the bases have apparently no optical rotation. It is believed that resolution has occurred since the melting points and solubilities of the salts in each case are different, and whilst polymorphism cannot be entirely excluded from consideration, we have not in any case observed any transformation of one salt to the other under a variety of conditions.

Pharmacological results. Using the modified version of the method of Ercoli and Lewis (3) for the determination of analgesic activity in rats the activities expressed in relation to morphine are: morphine, 1.0; amidone, 1.5; Prep. 1196, 0.97; Prep. 1779, 5.5; Prep. 1831, 3.5; and Prep. 1832, 7.9 by the subcutaneous route. Orally the activities expressed in relation to amidone were: amidone, 1.0; Prep. 1196, 1.4; Prep. 1779, 4.3; Prep. 1831, 3.9 and Prep. 1832, 5.1. The pharmacological results will be published in detail elsewhere. These results would suggest that Prep. Nu-1779 would be more closely related to dihydrodesoxymorphine-D than Prep. Nu-1196, since the former has an analgesic activity which is of the order of that of dihydrodesoxymorphine-D whereas the latter has only about $\frac{1}{5}$–$\frac{1}{10}$ of this activity. Hence the structure IVa is provisionally ascribed to *dl*-β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine and the structure IVb to the corresponding *dl*-α-compound.

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[1] These designations are given since the compounds have been submitted to pharmacological and clinical trials under these numbers.

Acknowledgment. Our thanks are due to Dr. L. O. Randall of the Pharmacological Division of these laboratories for the pharmacological results, and to Dr. A. Steyermark of the Microchemical Division for the elementary analyses.

EXPERIMENTAL

1,3-Dimethyl-4-phenyl-4-hydroxypiperidine. One liter of dry ether and 15 g. of lithium wire cut into small pieces were placed in a 3-liter round-bottom flask provided with a condenser, stirrer, and dropping-funnel. Bromobenzene (172 g.) was placed in the dropping-funnel and 10 cc. added at one time to the flask. Gentle warming was employed until the reaction started and then the bromobenzene was added from the dropping-funnel at such a rate that the ether refluxed vigorously. At the end of the reaction the dropping-funnel was rinsed with 100 cc. of ether and the flask cooled to −5°. One hundred twenty-seven grams of 1,3-dimethyl-4-piperidone (4) was added slowly from the funnel, maintaining the temperature at −5°. After the addition, the contents were stirred for 1 hour at room temperature. The flask was cooled in an ice-bath and 200 cc. of water was added slowly from the funnel with continued stirring. The ether layer was separated and dried over potassium carbonate. After the removal of the ether the residue was distilled *in vacuo* and the fraction boiling at 130°/2 mm. pressure was collected. This product was dissolved in 300 cc. of *n*-hexane (Skellysolve B), and on standing in the ice-box the product crystallized, yielding 150 g. of colorless crystals m.p. 72–85°. This is a mixture of diastereomeric alcohols. On one occasion, before distilling the crude mixture, it was kept at room temperature for 5 days. During that time crystallization of the α-form set in. The crystals were filtered, washed with Skellysolve B, and recrystallized from Skellysolve B, m.p. 103°; yield 75 g.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.09; H, 9.27
Found: C, 76.17; H, 9.05.

The filtrate was distilled in vac. at 130°/2 mm The distillate, a mixture of the α and β forms, was crystallized from Skellysolve B, m.p. 72–85°; yield 75 g.

1,3-Dimethyl-4-phenyl-4-propionoxypiperidine. 1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (229 g.) m.p. 72–85° was dissolved in a mixture of 350 cc. of pyridine and 350 cc. of propionic anhydride. The solution was refluxed for 3 hours and the solvents were distilled off *in vacuo* from a steam-bath using a water-pump. The residue, after cooling, was mixed with 200 cc. of water and basified with 20% sodium hydroxide solution to bring the *p*H to 9–10. The separated oil was extracted with ether, the ether solution dried over potassium carbonate, filtered, and hydrogen chloride gas bubbled in until no more hydrochloride separated. The solid, after drying in a vacuum desiccator over sodium hydroxide, was crystallized from about 600 cc. of acetone containing a little methanol. One hundred forty-five grams of colorless crystals, m.p. 212–214° was obtained in the first crop. This fraction has been named the α form.

Anal. Calc'd for $C_{16}H_{23}NO_2 \cdot HCl$: C, 64.53; H, 8.06.
Found: C, 64.58; H, 7.88.

The filtrate was concentrated to 250 cc. and allowed to stand in the ice-box overnight. A second crop of crystals was obtained which on recrystallization three times from acetone melted at 190–192°. This has been designated the β form; yield 107 g.

Anal. Calc'd for $C_{16}H_{23}NO_2 \cdot HCl$: C, 64.53; H, 8.06.
Found: C, 64.88; H, 7.99.

Resolution with d-tartaric acid. Five grams of β-*dl*-1,3-dimethyl-4-phenyl-4-propionoxypiperidine was converted to the free base with sodium carbonate. The oil was extracted with ether, and the ether solution dried over potassium carbonate. The ether was distilled off and the residue dissolved in 50 cc. of acetone containing 2.5 g. of *d*-tartaric acid. The solution was concentrated to 25 cc., and on standing in the ice-box crystallization occurred. The crystals were filtered off and recrystallized from methyl ethyl ketone (Prep. Nu 1831). Yield 3.5 g., m.p. 163–165°, $[\alpha]_D^{25}$ +13.1° (3% solution in methanol).

Anal. Calc'd for $C_{16}H_{23}NO_2 \cdot C_4H_6O_6 \cdot H_2O$: C, 55.94; H, 7.22.
Found: C, 55.98; H, 6.90.

The filtrate from the original crystallization was concentrated to dryness and the viscous residue was dissolved in methyl ethyl ketone. On standing in the ice-box crystallization occurred. The crystals were filtered and recrystallized two times from isopropanol (Prep. Nu 1832), m.p. 95–103° $[\alpha]_D^{25}$ +12.8° (3% solution in methanol).

Anal. Calc'd for $C_{16}H_{23}NO_2 \cdot C_4H_6O_6 \cdot H_2O$: C, 55.94; H, 7.22.
Found: C, 55.29; H, 7.20.

Resolution with l-malic acid. Seventeen and one-half grams of the β-*dl*-ester base was added to a solution of 9 g. of *l*-malic acid in 50 cc. of acetone. On standing in the ice-box crystallization occurred. The crystals were filtered off and recrystallized from acetone; yield 12 g., m.p. 134–135° $[\alpha]_D^{26}$ −2.26° (5% in H_2O).

Anal. Calc'd for $C_{16}H_{23}NO_2 \cdot C_4H_6O_5$: C, 60.76; H, 7.34.
Found: C, 60.83; H, 7.34.

The filtrate from the original crystallization was concentrated to dryness and the residue dissolved in 10 cc. of water. On standing in the ice-box crystallization occurred. The crystals were filtered off, dried, and crystallized from acetone, m.p. 114–115°; $[\alpha]_D^{26}$ − 2.74° (5% solution in water).

Anal. Calc'd for $C_{16}H_{23}NO_2 \cdot C_4H_6O_5$: C, 60.70; H, 7.34.
Found: C, 60.60; H, 7.43.

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